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Lifestyle factors and cognitive ageing in the Lothian Birth Cohort 1936: exploring the role of confounding by prior cognitive ability

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PhD by Research Publications

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Declaration

I declare that I have composed this thesis, that I have made a substantial contribution – clearly indicated – to each of the published papers, and that this work has not been submitted for any other degree or professional qualification.

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Abstract

With an increase in life expectancy, the number of older people affected by cognitive decline and dementia is rising, causing major, global public health concerns. However, there is substantial variation in the rate and magnitude of cognitive decline experienced among ageing individuals. Evidence suggests that many age-associated changes in cognitive functioning can be explained by modifiable lifestyle factors such as smoking, physical activity and diet choices. The weight of the evidence supports the promotion of a healthy lifestyle as an effective strategy for healthy cognitive ageing. Many epidemiological studies have drawn causal conclusions with regard to the positive and direct benefits of lifestyle, yet few have considered the possible confounding role of prior cognitive ability in explaining the lifestyle and cognition relationship in older age. Given the potential for reverse causation, whereby better prior cognitive functioning leads to a greater uptake of healthy behaviours rather than vice versa, it is a mechanism which should be studied, but rarely is.

The present thesis focuses on the possible confounding effect of prior cognitive ability on the cross-sectional relationships between lifestyle factors and cognitive ability domains in later-life. The core of the thesis is a series of independent, peer-reviewed (six first-author and one co-author) journal articles in the public domain. Data were derived from the Lothian Birth Cohort 1936 study ($n = 1091$), a sample of relatively healthy, community-dwelling men and women aged 70 years from Edinburgh, Scotland, for whom childhood (age 11) mental test scores are available. The lifestyle factors investigated were caffeine consumption, alcohol consumption, dietary patterns, body mass index, smoking, serum cholesterol, and physical activity. Cognitive function was assessed across five major ageing-related domains: age 70 IQ (based on the same test that was taken in childhood), general cognitive ability (g), processing speed, memory, and verbal ability. General linear models (ANCOVA) were adjusted for the following covariates: age; sex; childhood cognitive ability; and socioeconomic status (SES). Other potential covariates were additionally adjusted for as necessary.

Overall, the positive and significant associations observed between 'healthy' lifestyle factors and better cognitive functions at age 70 were consistent with previous research; their effect size was around 1% of the variance in cognitive tests scores. However, these relationships were markedly attenuated (by on average 80%) by a higher childhood

cognitive ability and adult SES; for the most part, associations were reduced to non-significance. None of the lifestyle factors were consistent predictors of performance across cognitive domains, though smoking avoidance, a physically active lifestyle, and moderate intake of alcohol, appeared to have the most potential.

The key novel finding of this thesis is that, in addition to having predictive value for lifestyle choices over 60 years later, cognitive ability at age 11 accounted for the majority of the cross-sectional associations between lifestyle factors and cognitive abilities in later-life. This finding is consistent with the theory of confounding or even reverse causation. That is, individuals with higher lifetime 'trait' cognitive ability may be more likely to adopt a lifestyle which protects against cognitive decline. Rather than a unidirectional or indirect effect of health behaviours on cognitive function, the present findings suggest there may be a dynamic cycle involving cognition, self-management of health and ultimate cognitive outcomes.

Lay Summary

Many studies have indicated that lifestyle factors such as diet, smoking, alcohol intake, and physical activity, are associated with better thinking (cognitive) skills in later-life. This is often thought to reflect a protective effect of a healthy lifestyle on mental abilities. However, these studies have not taken into account cognitive ability level from youth. The Lothian Birth Cohort 1936 (LBC1936) study is rare in having mental ability scores for participants from childhood (at age 11). The aim of this thesis was to identify lifestyle factors that might influence mental abilities in later-life in the LBC1936, after accounting for mental ability level in childhood, as well as other factors such as social class in adulthood. The studies on which this thesis is based found that those people with healthy behaviours tended to have better cognitive abilities, which supports previous findings. However, many of these associations were due to the fact that people with higher early-life mental abilities are more likely to adopt a healthier lifestyle later in life, rather than lifestyle factors influencing people's thinking skills. There were exceptions in that positive lifestyle choices such as smoking avoidance, physical activity and moderate alcohol intake, were related to better performance on some mental tests in later-life, irrespective of the other factors that were measured. The findings provide a step forward in understanding the lifestyle factors associated with cognitive ageing.

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1. Corley, J., Jia, X., Kyle, J. A. M., Gow, A. J., Brett, C. E., Starr, J. M., ... Deary, I. J. (2010)
Caffeine consumption and cognitive function at age 70: the Lothian Birth Cohort 1936 Study.
Psychosomatic Medicine, 72, 206–214. (thesis pp. 95–103)
2. Corley, J., Gow, A. J., Starr, J. M., & Deary, I. J. (2010)
Is body mass index in old age related to cognitive abilities? The Lothian Birth Cohort 1936 study.
Psychology and Aging, 25, 867–875. (thesis pp. 104–112)
3. Corley, J., Jia, X., Brett, C. E., Gow, A. J., Starr, J. M., Kyle, J. A., ... Deary, I. J. (2011)
Alcohol intake and cognitive abilities in old age: the Lothian Birth Cohort 1936 study.
Neuropsychology, 25, 166–175. (thesis pp. 113–122)
4. Corley, J., Gow, A. J., Starr, J. M., & Deary, I. J. (2012)
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Journal of Psychosomatic Research, 73, 132–138. (thesis pp. 123–129)
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Do dietary patterns influence cognitive function in old age?
International Psychogeriatrics, 25, 1393–1407. (thesis pp. 130–144)
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Serum cholesterol and cognitive functions: the Lothian Birth Cohort 1936.
International Psychogeriatrics, 27, 439–453. (thesis pp. 145–159)
7. Gow, A. J., Corley, J., Starr, J. M., & Deary, I. J. (2012)
Reverse causation in activity-cognitive ability associations: the Lothian Birth Cohort 1936. *Psychology and Aging*, 27, 250–255. (thesis pp. 160–165)

Preface

The objective of this thesis was to examine the role of lifestyle factors in relation to cognitive ageing, with particular emphasis on the influence of lifetime ‘trait’ cognitive ability, in cognitively healthy older adults. The thesis presents a series of seven studies, in the form of six first authored and one co-authored papers published between the period 2010—2015, which form a coherent whole.

Change and decline in cognitive abilities typically accompany ageing. Identifying modifiable environmental exposures that predict better cognitive functioning in older people potentially contributes to reducing the risk of cognitive decline and dementia which undermine quality of life for the rapidly increasing older proportion of the population. Lifestyle factors such as dietary intake, smoking, alcohol, and physical activity, potentially influence older-age cognitive status via nutritional, cerebrovascular and cardiovascular mechanisms (Alagiakrishnan, McCracken, & Feldman, 2006; Esiri et al., 1999) that support brain health and functioning, and by influencing risk of chronic diseases that in turn predict poorer cognitive outcomes in older age.

A serious impediment to understanding the role of lifestyle factors in older age cognitive health is ascertaining to what degree observed cognitive function in older people reflects lifetime cognitive function (the trait level, often called premorbid or prior cognitive ability), rather than any cognitive decline experienced with age (the trajectory). Due to data constraints, the majority of research that examines associations between lifestyle factors and older-age cognitive performance, has utilised either a baseline measure of cognitive ability from the first assessment (e.g. in early older age) or a proxy measure of lifetime cognitive ability derived from vocabulary tests such as the National Adult Reading Test (NART), for example. Very few studies have a direct measure of cognitive ability or IQ from early in life.

The studies on which this thesis is based, were carried out in a sample of older adults, known as the Lothian Birth Cohort 1936 (LBC1936; Deary et al., 2007; Deary, Gow, Pattie, & Starr, 2012). The LBC1936 study, which began in 2004, is a longitudinal cohort study investigating the determinants of cognitive ageing in cognitively healthy older adults, aged about 70 at baseline. This sample share the same year of birth, and are relatively rare in having a measure of cognitive ability at age 11. The dataset is rich in demographic, cognitive, health and medical data. Although the research for this

thesis examines 'normal' cognitive ageing, it should be emphasized that the potential findings are relevant to informing prevention strategies for pathological cognitive ageing. It has been demonstrated in numerous studies that those who later develop Alzheimer's disease consistently perform more poorly on cognitive tests during the prior dementia-free period from many years earlier (Elias et al., 2000; Twamley, Ropacki, & Bondi, 2006). Thus, the identification of modifiable environmental factors (including lifestyle factors) that predict differential cognitive outcomes offer potential pathways to prevention, or at least delay, the debilitating clinical symptoms of dementia and decline (Singh-Manoux & Kivimaki, 2010).

The scope of this thesis straddles a number of research disciplines including psychology, epidemiology, nutrition, neuroscience and medicine. A brief overview of the thesis structure follows. The thesis is presented in three parts. Part I is a general literature review. It commences with the public health importance of cognitive changes with age, an overview of cognitive ageing, and the factors associated with individual differences in cognitive ageing. Chapter 2 focuses on the potential influence of lifestyle and health-related factors on cognitive ageing, drawing on the previous literature to date. An extensive body of research suggests that the 'big four' factors, namely, diet, alcohol, smoking and physical activity, are correlates and predictors of cognitive functioning in ageing. In addition to a healthy diet, moderate alcohol consumption, smoking avoidance, and physical activity, the literature suggests that a healthy body mass index and lower cholesterol levels may also, in part, predict later-life cognitive outcomes. The appeal of studying factors like these is in part due to the fact that these behaviours are amenable to modification. The potential impact of lifestyle on cognitive ageing has led to a profusion of population studies reporting positive effects of a healthy lifestyle not generally supported by intervention studies and clinical trials. One possible reason for this discrepancy is reverse causation where prior intelligence predicts both choice of lifestyle pursuits and later-life cognitive outcomes. Consequently, Chapter 3 presents an overview of findings from studies that have examined the effect of IQ in early-life on the adoption of health behaviours in later-life and discusses the theories of confounding and reverse causation as potential models for explaining the observed associations between healthy lifestyles and healthy cognitive ageing. Investigating reverse causation is of central importance and it has implications for those developing interventions to reduce cognitive decline. The influence of socioeconomic status on lifestyle and cognition is also introduced here.

The hypothesis which is tested throughout the thesis is that lifestyle-cognition associations in older age, in part reflects stable intelligence differences, rather than a protective effect of lifestyle. Therefore, Part I sets the context for assessing the contribution of lifetime stable IQ differences to the relationship between potential environmental predictors, here, lifestyle factors, and individual differences in older-age cognitive outcomes. To assert that lifestyle is cognitively advantageous, these effects must persist after a valid measure of prior cognitive ability is accounted for (Deary & Gow, 2008).

Part II describes the methodology adopted throughout the thesis including the general aims and approach, dataset used, the measurement of the lifestyle factors, the measurement of the cognitive outcomes and covariates, and the statistical models to examine the associations between lifestyle and cognition. Each study examines the cross-sectional associations between a lifestyle factor and cognition at baseline, when participants were approximately age 70. They use a similar analysis technique, namely, general linear models, throughout. Relevant covariates are included where appropriate as indicated by previous literature. The rationale for each study, representing seven papers, is briefly discussed. The first three papers focus on dietary intake, specifically, caffeine consumption, alcohol consumption, and dietary patterns. Participants who completed a food frequency questionnaire at baseline were included in these studies. The following three papers examine body mass index, smoking, and cholesterol levels in relation to cognitive function, in the entire LBC1936 cohort. The seventh and final paper of the thesis is a co-authored article on one of the most widely studied lifestyle factors, physical activity.

Part III provides a general summary of the main findings from each published paper and a concluding discussion. This series of seven studies aimed to examine, for the first time, whether the relationship between lifestyle and cognition in later-life is an artefact of confounding by lifetime IQ differences (measured directly) or whether there are real, independent contributions from healthy behaviours to accounting for variance in cognitive ageing. Methodological issues and limitations are acknowledged and addressed. The final part of this section considers the contribution this body of work makes to the current literature, the implications of this research, and future planned directions.

PART I: LITERATURE REVIEW

Chapter 1 - Cognitive Ageing

1.1 Introduction

Understanding human cognitive ageing is one of the greatest scientific challenges to society today. One of the striking aspects of cognitive ageing is the marked degree of individual variation that exists among older adults; some decline far more, and some far less, than the average (Deary, Whiteman, Starr, Whalley, & Fox, 2004; Salthouse, 2006; Schaie, 2005a). It is likely that a number of factors are responsible for the heterogeneity in cognitive ageing. Among them, empirical evidence suggests that various lifestyle factors such as diet, smoking and physical activity, potentially predict individual differences in cognitive ability measures amongst cognitively healthy older people free from dementia or cognitive impairment (Franklin & Tate, 2009; Hertzog, Kramer, Wilson & Lindenberger, 2009; Lee, Back, Kim, Kim et al., 2010; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Lifestyle factors are of interest to researchers and clinicians because they often involve behaviours which can be modified by individuals. Interventions which encourage a healthy lifestyle may help ameliorate cognitive decline. Although the idea that older adults can play a role in their cognitive health is intuitively appealing, the evidence from systematic reviews is equivocal.

1.2 The public health importance of cognitive ageing

The current thesis addresses an important public health issue that is expected to affect millions of people in the near future: cognitive health in later-life. For most, losing one's cognitive abilities, especially memory, is feared more than physical disability (Martin, 2004) and is associated with a poorer quality of life (Plassman et al., 2010), not to mention increased health care costs (Brayne, 2007). Issues related to cognitive ageing are becoming critically important to consider as human longevity increases and the proportion of the older adult population grows. Currently, there are 11.4 million people in the UK aged 65 years old and over (UK Office for National Statistics, 2015). Recent projections are for 5½ million more older people in 20 years' time, and by 2050, the number will have nearly doubled to around 19 million (Cracknell, 2010). As Brayne

(2007, p.233) notes, “in many countries, the older population now faces the prospect of spending a quarter of their lives aged over 65”. Normal age-related cognitive decline has been associated with decreases in instrumental activities of daily living, such as food shopping, cooking, medication management, financial management, and with other activities such as reading and travelling (Dodge et al., 2008, Royall, Palmer, Chiodo, & Polk, 2005; Tucker-Drob, 2011). Ameliorating cognitive decline is crucial in order to extend independent living and promote active and healthy ageing. The identification of preventative strategies to maintain cognitive health can be considered a key priority for the reduction of age-associated disability and morbidity (Depp, Harmell, & Vahia, 2012).

1.3 Cognitive and brain changes with ageing

It is widely accepted that some cognitive abilities decline on average with normal ageing. It is also recognised that there are large individual differences in the rate and magnitude of decline among ageing individuals (Hofer & Alwin 2008; Hedden & Gabrieli, 2004). Some people show marked cognitive declines, whereas others maintain cognitive skills relatively well into later-life (Birren & Schaie, 2005a; Deary, Penke, & Johnson, 2010). On average, aspects of memory, speed of information processing, reasoning, and executive functioning, abilities which require fluidity in neuropsychological processes, decline in a similar manner to that of age-related changes in physical functioning (Schaie, 2005a). At the same time, some verbal and numerical abilities and general knowledge, abilities representing the application of accrued knowledge (aspects of crystallised cognitive ability), are well retained into later-life (Lezak, 2004).

Even healthy, older community-dwelling individuals will experience some degree of mental decline, just as their physical capacities such as lung function, walking speed and muscle strength, have diminished since youth. In one of the landmark cognitive ageing studies – the Seattle Longitudinal Study – noticeable mean declines were generally apparent across a range of diverse abilities tested by ages 50 to 60 years and, by the mid-seventies, declines in all abilities were evident. Perceptual speed exhibits an almost linear decline from young adulthood onwards (Schaie, 2005a). These declines are within the realm of normal or non-pathological cognitive ageing, which is the focus of the current thesis. Use of the term ‘normal’ distinguishes non-pathological age-related cognitive decline from the pathological disorders, mild cognitive impairment

(MCI) and dementia. These disorders represent the clinically diagnosable end of the cognitive decline spectrum. Nevertheless, studying the 'milder' end of the spectrum is important as individuals with cognitive decline are at increased risk for progressing to MCI and dementia (Sperling et al., 2011).

Changes in cognitive functions are related to structural and functional changes in the brain, particularly in the frontal and medial temporal regions (Drag & Bieliauskas, 2010). In addition to brain atrophy, the ageing process affects the integrity of white matter pathways, resting blood flow, and the metabolic rate of brain oxygen consumption. The integrity and volume of white matter and the extent of white matter hyperintensities have been the focus of much recent research, as contributors to normal cognitive ageing (Booth et al., 2013; Penke, Muñoz Maniega, Houlihan et al., 2010; Penke, Muñoz Maniega, Murray et al., 2010; Penke et al., 2012; Aribisala, Valdés Hernández et al., 2013; Valdes Hernandez et al., 2013; Maniega et al., 2015). For example, white matter changes, primarily in the frontal cortex, are associated with slowed information processing speed (Hedden & Gabrieli, 2004; Penke, Muñoz Maniega, Murray et al., 2010; also see Madden, Bennett, & Song, 2009) and memory (Hedden & Gabrieli, 2004).

Although there are age-related declines in cognitive functions that begin early and progress as people age, not all adults experience ageing in the same way. This raises the question, which factors account for peoples' differing cognitive ageing trajectories and ultimately, is there a recipe for 'healthy' cognitive ageing?

1.4 Factors associated with individual differences in cognitive ageing

Despite major research efforts, there is still no comprehensive account to explain the risks for cognitive decline (Deary, Corley et al., 2009; Whalley, Dick, & McNeill, 2006). While further research is needed, current evidence, primarily from observational and epidemiological studies, suggests that a range of both genetic and environmental factors influence individual differences in cognitive trajectories and cognitive decline during ageing (Hertzog et al., 2009; Mangialasche, Kivipelto, Solomon, & Fratiglioni, 2012).

1.4.1 Prior cognitive ability: a lifelong stable trait

The single most important predictor of the level of cognitive function in later-life is early-life cognitive function. Individual differences in cognitive function across the life

course are highly stable and trait-like (Deary, Whiteman et al., 2004; Gow et al., 2011). Previous estimates indicate that approximately 50% of the reliable variance in IQ scores in older age, even up to almost age 80, is explained by cognitive function in youth (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman et al., 2004; Gow et al., 2011). Children develop greater intelligence over time but tend to maintain the same rank order (Deary, Penke et al., 2010).

Longitudinal studies of the elderly that commence within older age are beset with difficulties in ascertaining to what degree observed cognitive function reflects already present declines and life-long levels (Johnson, Gow, Corley, Starr, & Deary, 2010). Cognitive function measured at a static point in older age cannot be used as a reliable indicator of cognitive ageing. Rather, individuals' performance on a mental test reflects both lifetime cognitive function (the trait level, often referred to as premorbid or prior cognitive ability), as well as the amount of cognitive decline, if any, experienced with age (the trajectory).

Though the potentially modifiable determinants of late-life cognitive ability are the focus of much research, these cannot be identified definitively without knowing the extent to which later-life cognitive abilities differ from those in earlier life. It is ideal to assess cognition first in youth, when cognitive assessment is unaffected by the processes of age and age-related illness, and again in later-life. Longitudinal cohort studies with a true measure of cognitive change across the life course are optimal to elucidate the effects of potential predictors of cognitive ageing (e.g. Schaie, 2005b).

1.4.2 Genetic factors

Of course, some of the factors influencing individual differences in cognitive ageing trajectories are likely to be essentially 'fixed' i.e., genetic factors. That children maintain the same rank order of intelligence over time (Deary, Penke et al., 2010), is largely due to genetic influences on general intelligence, usually referred to as *g*. In fact, heritability of general intelligence increases with age, from about 30% in childhood to as much as 70-80% in adulthood. A Dutch twin study used repeated assessments of general intelligence to show that the heritability of general intelligence increases with age, even within the early years, from age 5 (26%), age 7 (39%), age 10 (54%), to age 12 (64%). Broad domains of cognitive ability, such as verbal abilities, generally show similar amounts of genetic influence, although evidence suggests that the genetic influences on memory tend to be smaller (Bartels, Rietveld, Van Baal, & Boomsma, 2002).

Elucidating the heritability of intelligence is highly informative in itself, but discovering genetic contributions to cognitive change or trajectory in later-life, is crucial to the study of cognitive ageing. Possession of the E4 allele of the gene for apolipoprotein E (*APOE*) is now considered a well-established risk factor for Alzheimer's disease (Corder et al., 1993) and has been implicated in both the age of onset (Slooter et al., 1998), and the rate of cognitive decline associated with this disease (Cosentino et al., 2008). *APOE* E4 allele carrier status is also associated with an increased rate of cognitive decline in domains such as memory (Blair et al., 2005; Caselli et al., 2009) and abstract reasoning (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003), in non-pathological cognitive ageing (Schiepers et al., 2012), as well as decreased general cognitive functioning (Davies et al., 2011; Fillenbaum et al., 2001; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999).

Despite the high heritability of intelligence, other than *APOE*, no genes have yet been identified that have been conclusively linked to variation in cognition or cognitive decline with age in healthy, normal individuals (Payton, 2009). The emerging view of genetic influences on intelligence is that it is likely that a large number of genetic variants have small effects (Deary, Penke et al., 2010). The *APOE* E4 effect, for example, accounts for between 1% and 2% of the variance in cognitive change between age 11 and age 79 (Deary et al., 2002; Deary, Yang et al., 2012). Using data from the Lothian Birth Cohorts of 1921 and 1936, and the Aberdeen Birth Cohort of 1936, it has been estimated that 24% of lifetime cognitive change was due to genetic factors (Deary, Yang et al., 2012). These important findings endorse future searches for genetic mechanisms of cognitive change across the life course. They also suggest the importance of environmental contributions to lifetime cognitive change.

1.4.3 Environmental and health factors

Multiple behavioural, social and economic factors have been associated with differential cognitive ageing in observational studies (see Plassman et al., 2010; McKee & Schüz, 2015). These potential risk and protective factors range from education, socioeconomic status, midlife hypertension, social contact and social support, occupational attainment, working environments, job complexity, sleep, and intrinsic factors such as psychological stress, depression symptomatology, self-rated health and perceptions of control (Mangialasche et al. 2012; Stern, 2012; Barnes & Yaffe 2011;

McKee & Schüz, 2015). It is worth noting that many of these environmental factors have genetic contributions too.

With age comes an increased risk for multiple chronic diseases and widespread use of medications. Vascular disease is a well-established risk factor for MCI and dementia (Zylberstein et al., 2011). Studies over the last decade indicate that normal cognitive ageing may partly be caused by illness such as vascular disease; the individual disease entities of stroke, myocardial infarction and peripheral vascular disease are all associated with cognitive decline within old age in non-demented people (Rafnsson, Deary, Smith, Whiteman, & Fowkes, 2007). Risk factors for cardiovascular disease such as hypertension (Qiu, Winblad, & Fratiglioni, 2005), ankle-brachial pressure (Price et al., 2006; Laukka, Starr, & Deary, 2014), and hypercholesterolaemia (van Vliet, van de Water, de Craen, & Westendorp 2009) are associated with cognitive decline, as are metabolic factors such as diabetes (Cukierman, Gerstein, & Williamson, 2005; Knopman, Mosley, Catellier, & Coker, 2009) and the metabolic syndrome (Yaffe, 2007). It has been suggested that much of the variance between people in cognitive functioning in older age is attributable to poor health (Spiro & Brady, 2011).

With the “continued greying of the industrialized world” (McGue, Skytthe, & Christensen, 2014, p.775), a key goal is to identify any modifiable environmental factors that account for differences in age-related cognitive decline. Such factors could be promoted or discouraged as appropriate, and manipulated via interventions to delay or lessen cognitive decline. There has been a concerted research effort in recent years to study these mutable factors, and this research is discussed in the following chapters.

1.4.4 Interplay between genetics and environment

Although the focus of this thesis is environmental, specifically lifestyle, influences on cognitive function in later-life, it is important to remember that the antecedents of an individual’s cognitive ageing trajectory are the result of numerous complex genetic and environmental interactions across the life course, including educational attainment, demographic factors and health status, with influences reaching as far back as the prenatal environment (Benton, 2010). Although we cannot change our genes, genetic influences are not ‘fixed’ in that they can be modified by physiological and environmental influences (Ben-Shlomo & Kuh, 2002). To give an example, Vasilopoulos et al. (2012) found that untreated hypertension suppresses normal genetic influences on individual differences in certain domains of cognition prior to the emergence of

hypertension-related effects on cognitive performance. It has been suggested that genetics play a large role in development of age-related brain changes or disease-related pathology, and that environmental factors play a larger role in the expression of cognitive impairments (Mortimer, Borenstein, Gosche, & Snowden, 2005; Stern, 2012).

To summarise thus far, certain factors are known to affect age-related cognitive decline. Beyond age, genetic factors, and stable IQ differences, allowing for error variance, it is likely that around 40% of variance in IQ scores in older age is determined by extrinsic factors such as lifestyle. Determining this unexplained variance is paramount in the field of cognitive ageing research. Although individual differences in 'trait' intelligence tend to remain fairly stable from childhood and throughout the life course, developmental processes and environmental circumstances contribute to less-than-perfect stability of cognitive ability. However, the problem of identifying the demographic, biological, and psychosocial factors that can help people maintain or enhance their cognitive health is not straightforward.

Chapter 2 - Lifestyle Factors and Cognitive Ageing

2.1 The potential influence of lifestyle factors

The observation that some individuals live into old age with minimal decline, together with increasing evidence for brain plasticity in response to environment and experience across the life course, has sparked considerable global interest in understanding how older adults can maintain cognitive function; specifically, whether engagement in lifestyle activities can decrease risk for cognitive decline or dementia. Accumulating evidence from epidemiological studies suggests that many age-associated changes in cognitive functioning can be explained by such modifiable lifestyle factors such as diet choices, alcohol consumption, smoking, physical activity and weight (see Lee, Back, Kim, Kim et al., 2010). These constitute behavioural risk factors known to influence health. It is estimated that in the general population, lifestyle and health-related risk factors may contribute to almost half of dementia cases (Barnes & Yaffe, 2011) suggesting that further investigation of this constellation of risk factors is critical to understanding risk of cognitive ageing and developing effective prevention strategies.

Empirical studies to date suggest that cognitive performance in older age can be maintained by health-promoting behaviours such as a healthy diet (Kang, Ascherio, & Grodstein, 2005; Morris, Evans, Tangney, Bienias, & Wilson., 2006; Luchsinger & Mayeux, 2004), especially a Mediterranean-style dietary pattern (Féart et al., 2009; Féart, Samieri, & Barberger–Gateau, 2010; Scarmeas, Stern et al., 2009; Tangney et al., 2011) moderate alcohol consumption (Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005; Peters, Peters, Warner, Beckett & Bulpitt, 2008), physical activity (Kramer, Erickson & Colcombe, 2006; Jedrzejewski, Lee, & Trojanowski., 2007; Gow et al., 2011; van Gelder et al., 2004), maintaining a healthy weight (Cournot et al., 2006; Dahl et al., 2010; Elias, Elias, Sullivan, Wolf, & D'Agostino., 2003), and not smoking (Anstey, von Sanden, Salim, & O'Kearney., 2007; Sabia, Marmot, Dufouil, & Singh-Manoux., 2008). There are also risk factors for cognitive decline and dementia that are modifiable by medication. An example of these risk factors is hypercholesteremia (the presence of high cholesterol levels in the blood), which has been shown, like hypertension, to increase the risk of cognitive decline and dementia (Anstey, Lipnicki, & Low, 2008; Qiu et al., 2005). These conditions are usually treated for the prevention of cardiovascular disease. The taking of medications to prevent such conditions is also a health behaviour

that ultimately may contribute to brain health and prevention of later cognitive decline. Emerging from this body of work is the concept of 'successful ageing' (Franklin & Tate, 2009; Yaffe et al., 2009).

The available evidence to date suggests that these health behaviours, particularly smoking, sedentary lifestyle, and poor dietary choices, predict poorer cognitive function (level), faster cognitive decline (trajectory) (Whalley, Fox, Deary, & Starr, 2005; van Gelder et al., 2004; Deary, Corley et al., 2009) as well as a higher risk of dementia (Lee, Back, Kim, Kim et al., 2010; Phung, Andersen, Kessing, & Waldemar, 2006). However, the majority of support derives from cross-sectional studies; comparatively little is known about the longitudinal effects of these behaviours on cognitive decline. Furthermore, a large systematic review by Plassman et al. (2010) concluded that there is as yet, insufficient evidence from which to draw firm conclusions about lifestyle factors and their association with cognitive decline, or make recommendations for interventions. Some of the factors highlighted in Plassman et al.'s review include age, in terms of the timing of exposures and their different effects, at different time points throughout life. Another key issue is that it is often unclear whether the exposures studied are determined a priori, by clinical relevance, or previous work in that area. Furthermore, the modest effect size frequently reported in the studies reviewed raises questions about the robustness of the findings and doubts about statistical significance versus what is often called clinical significance. Their review concluded that, given the problems inherent in running intervention trials, efforts should be made to obtain quality evidence from further well-designed observational studies (Plassman et al., 2010).

A full discussion of the relevant literature can be found in each of the seven published papers submitted here. Other psychosocial factors potentially influencing cognitive ageing trajectories such as cognitive activities, sleep, perceptions of control, social support and social contact, are beyond the remit of this thesis and are therefore not reviewed. In the next sections, the potential neurobiological mechanisms by which lifestyle and cognitive function may be related, are discussed, and the methodological issues arising from the current literature.

2.2 The mechanisms linking lifestyle and cognitive function in older age

In general, observational studies support a link between healthy behaviours and successful cognitive ageing. The core hypothesis linking health behaviours to cognitive

ageing involves cerebro- and cardiovascular diseases as mediators (see Lee, Back, Kim, Kim et al., 2010; Alagiakrishnan et al., 2006) and their association with cognitive impairment is well established (Debette et al., 2011; Kivipelto et al., 2001; Plassman et al., 2010; Rafnsson et al., 2007). Indeed, the more vascular risk factors a person has, the greater the risk of developing Alzheimer's Disease (Kivipelto et al., 2005; Luchsinger et al., 2005). Lifestyle factors are known to promote brain white matter (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010) and grey matter (Erickson et al., 2010; Ho et al., 2011) integrity in older adults by potentially increasing neurogenesis and angiogenesis, as well as reducing cerebrovascular risk factors (Kramer et al., 2006).

Some vascular risk factors can be controlled through proper diet and nutrition (Lee, Back, Kim, Kim et al., 2010). A change in diet can result in a change in health variables such as hypertension, diabetes, hyperlipidaemia, and obesity (Rees et al., 2013; Santos, Esteves, da Costa Pereira, Yancy, & Nunes, 2012), which are often connected. Another way to consider the role of diet and nutrition in maintaining brain health is from a nutrient based perspective. Micronutrients are thought to be important for cognitive health because they play a role in processes such as oxidative stress and inflammation, which are known to play a role in age-related brain changes (Baierle et al., 2015; Deary, Corley et al., 2009). Aspects of a healthy diet such as high levels of antioxidants found in fruits and vegetables may help to protect against neuronal damage (Kang et al., 2005). Key components of the Mediterranean diet have biologically plausible mechanisms for suspected neuroprotective effects that have been demonstrated in some epidemiologic studies (Scarmeas, Stern et al., 2009); it is associated with lower inflammatory and oxidative load via nutrients, monounsaturated fatty acids and polyphenolic compounds (Frisardi, Panza, Solfrizzi, Seripa, & Pilotto, 2010; Serhan, 2011). There is evidence to suggest that polyphenols (found in dark chocolate and other Mediterranean diet foods) stimulate neurogenesis (Dore, 2011). Caffeine in coffee and other foods has specific neuroprotective effects on adenosine receptors in the brain and neuroprotective antioxidant activity (Tebano et al., 2008; Rahman, 2009). Although chronic alcohol consumption has been associated with neurodegenerative diseases, moderate alcohol consumption may protect against cognitive impairment by increasing HDL cholesterol levels and fibrinolytic factors that lowers platelet aggregation, enhancing insulin sensitivity, reducing inflammatory response, and preventing oxidative damage to the brain (Peters et al., 2008). Polyphenol compounds in red wine

may also inhibit LDL oxidation and thrombosis independently of alcohol (Saremi & Arora, 2008).

The effect of being overweight or obese on cognitive health may be due to a direct effect of adiposity on the neuroendocrine system or mediated through other components of the metabolic syndrome such as hypertension and type II diabetes (Beydoun, Beydoun, & Wang, 2008). In addition, adipose tissues secrete inflammatory proteins such as leptin which could affect neurodegeneration (Zeki Al Hazzouri, Haan, Whitmer, Yaffe, & Neuhaus, 2012).

Smoking is a well-established characterised cardiovascular risk factor and, possibly mediated by oxidative stress, inflammation and atherosclerosis, is known to increase the risk for neurodegeneration (Swan & Lessov-Sclaggar, 2007). Neuroimaging studies indicate that smoking may lead to both macro- and microvascular cerebral damage (Debette et al., 2011; Gons et al., 2011).

Physical activity is thought to enhance cognitive function by increasing cardiovascular fitness and cerebral perfusion, and possibly by stimulating neurogenesis (Lee, Back, Kim, Kim et al., 2009). Other protective effects include a reduction in inflammation and depressive symptoms (Ahlskog, Geda, Graff-Radford, & Petersen, 2011; Dishman et al., 2006).

High cholesterol is a proven risk factor for cardiovascular disease (Klag et al., 1993; Martin, Hulley, Browner, Kuller, & Wentworth, 1986). Low levels of the 'good' high-density lipoprotein (HDL) and elevated 'bad' low-density lipoprotein (LDL), together with elevated triglycerides, contribute to arterial plaque deposition in the elderly (Arai & Hirose, 2004; de Freitas et al., 2011). This in turn leads to atherosclerosis and the risk of myocardial infarction and acute ischaemic stroke or silent brain infarcts (Fjell & Walhovd, 2010). Detrimental effects of low (total) cholesterol on cognitive performance have been reported in previous studies (Benton, 1995; Muldoon, Ryan, Matthews, & Manuck, 1997; Mielke et al., 2005; Reitz, Luchsinger, Tang, Manly, & Mayeux, 2005). Low cholesterol levels often accompany chronic diseases, poor intake or absorption of nutrients, and diagnosed and occult malignancies (Fiorenza, Branchi, & Sommariva, 2000), which in turn may be associated with poorer cognitive performance. Low serum cholesterol and poorer cognitive functioning may also be

related because neuronal cells require total cholesterol for normal metabolic processes (Muldoon, Flory & Ryan, 2001).

Lifestyle and health-related behaviours are, unsurprisingly, powerful determinants of morbidity and mortality worldwide (Ford, Zhao, Tsai, & Li, 2011). Smoking, alcohol consumption, poor diet and physical inactivity are among the top ten leading risk factors for death and disability in intermediate- and high-income countries (World Health Organisation, 2009). Lifestyle-related, degenerative chronic diseases such as type 2 diabetes may be prevented by adopting healthy behaviours. For example, physical activity lowers the risk of diabetes, cancer and osteoporosis as well as all-cause and cardiovascular death (Warburton, Nicol, & Bredin, 2006). Engaging in the four key healthy behaviours, being physically active, not smoking, moderate alcohol consumption and consuming at least five portions of fruit and vegetables per day, may add up to 14 years to one's life (Khaw et al., 2008).

Health behaviours may be directly or indirectly associated with cognitive decline. For example, physical activity may have both indirect and direct effects on brain function (Kramer et al., 2003). The indirect effects are through the benefits of exercise for reducing other risk factors which have been associated with both cognitive decline and dementia such as obesity (Andre & Wolf, 2007), diabetes and hypertension (Qiu et al., 2005). The direct effects of physical activity may result from increased cerebral blood flow and oxygenation (Colcombe et al., 2003). Regardless of the precise underlying mechanisms, the implication is that some of the predictors of successful ageing are in many ways under personal control.

Chapter 3 - An Evaluation of the Current Literature: **Methodological Issues and Theoretical Considerations**

3.1 General methodological Issues

Efforts to identify lifestyle factors that are associated with cognitive ageing are subject to limitations which hamper data interpretation. Many of the effects are small, and studies report associations between lifestyle factors and different domains of cognitive functioning. Not all findings have been replicated. Several reviews have commented that the quality of the evidence is often low and have called for more long-term cohort studies before conclusions can be drawn with confidence about the role of lifestyle factors in cognitive ageing (Plassman et al., 2010; Williams, Plassman, Burke, & Benjamin, 2010). In addition, there are wide differences in methodologies used in terms of the measurement of health behaviours and the measurement of cognitive function and cognitive change. Many studies rely upon brief (crude) tests of global cognition such as the Mini-Mental State Examination (MMSE) which are not as sensitive as comprehensive neuropsychological test batteries, do not test specific domains of cognition well or at all sometimes, and are subject to ceiling effects (Leroi, Sheppard, & Lyketsos, 2002). Sample size, cohort age and age-range, and attrition (Ferrie et al., 2009), as well as cultural differences, also contribute to the variation among studies. Issues related to the directionality of the association between lifestyle activities and cognitive functioning are fundamental and described below.

3.2 The confounding effect of prior ability

Many studies reporting a so-called beneficial or detrimental 'effect' of lifestyle factors or health behaviours on cognitive function in later-life, have done so without any knowledge of the studied individuals' cognitive ability history (i.e. from youth). That is, what one really wants to know is whether the lifestyle factor accounts for some cognitive test score variance in older age after adjusting for prior cognitive ability variance. Without this information, studies may erroneously ascribe a causal influence of a lifestyle factor. For example, Whalley and colleagues (2004) identified a potential protective effect of taking vitamin supplements on cognition in older age. However, further analyses revealed that those who took supplements had a higher intelligence in childhood and adulthood (Whalley, Fox, Whale, Starr, & Deary, 2004). This example, and others in the literature, provides evidence for confounding by prior cognitive ability.

Many population studies of cognitive ageing attempt to control for prior cognitive functioning by relying on estimates derived from proxies such as educational level and cognitive tests performed contemporaneously with the cognitive outcomes such as word-reading or vocabulary (see Bright, Jaldow, & Kopelman, 2002; Deary & Johnson, 2010; Spinks et al., 2009). Although widely accepted in the literature, estimates of premorbid/prior intelligence are less than satisfactory because they could reflect some of the environmental conditions hypothesized to contribute to cognitive decline (Deary & Johnson, 2010; Johnson et al., 2010). As with any estimate, it is susceptible to error. Spinks et al. (2009) noted how poorly IQ proxy measures, including a version of the NART, performed at the tails of the IQ distribution. The proxy measures consistently overestimated the IQ of low-functioning individuals and underestimated the IQs of high-functioning individuals. Furthermore, though education and occupation are thought to be influences on cognitive ageing, it must be noted that childhood cognitive function is a substantial predictor of both of these factors (Deary & Gow, 2008; Deary & Johnson, 2010; Strenze, 2007). Examination of any lifestyle-cognition relationship, benefits from knowledge of cognitive ability obtained in early-life (childhood), for several reasons. First, it is useful to have a measure of cognitive function at an early age, before the adoption of adult health behaviours such as smoking, and before the onset of adult chronic illnesses that can affect cognitive ability. Second, it is useful to have a measure of cognitive function before secondary education brings about educational experience heterogeneity, and before adult socioeconomic status (SES) is attained. Thirdly, it allows an assessment of people's differences in cognitive change across the life-course.

3.3 Reverse causation in lifestyle-cognition associations

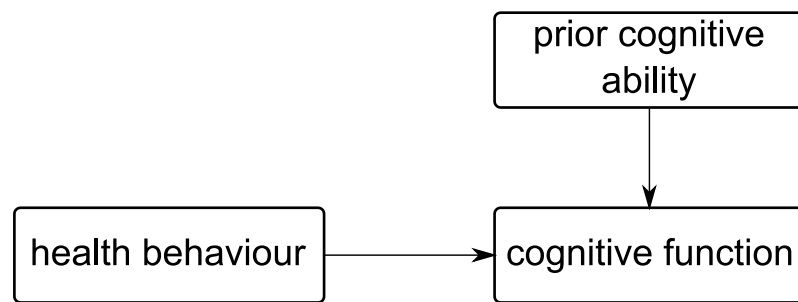
The previous section identified that prior ability may confound some determinants of cognitive ageing but it may also precede and predict these very same factors (Gow et al., 2011). This is often termed reverse causation, in which there is modification of the independent (predictor) variable by the dependent (outcome) variable (Lawlor, Hart, Hole, & Davey Smith, 2006).

An alternative explanation for the lifestyle-cognition associations observed in epidemiological investigations is that people with higher childhood intelligence are those who, at an older age, are cognitively brighter and more likely to adopt a healthy lifestyle. For example, individuals who adhere to a 'healthy' dietary pattern may

perform better on multiple tests of cognitive function measured in later-life, but much of this association may be due to the fact that people with a higher early-life IQ are more likely to have a healthy diet (Batty, Deary, Schoon & Gale, 2007a; McNeill et al., 2011). Further evidence suggests that those with a higher IQ in youth are also more likely to be physically active in adulthood (Batty & Deary, 2004; Anstey, Lowb, Christensen, & Sachdev, 2009), to have a healthy BMI (Batty, Deary, Macintyre, 2007; to drink alcohol moderately (Espeland et al., 2005; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005) and to avoid smoking (Batty, Deary, Macintyre, 2007; Kubicka, Matejcek, Dytrych, & Roth, 2001; Taylor et al., 2003). These findings support the hypothesis of reverse causation, whereby better cognitive functioning leads to greater adherence to healthy lifestyle practices rather than vice versa. Figure 1 demonstrates: (1) the direct causal relationship typically assumed in most epidemiological studies in this area of research, and: (2) the hypothesis of reverse causation tested in the current thesis, in which prior cognitive ability might be a cause of the supposed 'cause' of cognitive ability in older age. Essentially, people with a higher early-life IQ may be more likely to engage in a lifestyle which protects against cognitive decline in the long-term. This supports the idea that cognition may literally influence the extent to which individuals manage their own risk for cognitive decline (Anstey et al., 2009).

Reverse causation is a major issue for health outcomes in general but especially with regards to cognitive decline and dementia, due to the prolonged prodromal phase (Yaffe, Hoang, Byers, Barnes, & Friedl, 2014). The possibility that associations between healthy behaviours and improved cognitive performance might be wholly or partly attributable to prior cognitive ability predicting both, has implications for public health campaigns and interventions, to reduce cognitive decline. Given the potential for reverse causation, it is worryingly underreported and often not, or not able to be, tested. Insufficient attention has been paid to the possibility of reverse causation partly as childhood IQ records are rarely available in studies of adult cognitive ageing.

(1) Causation



(2) Confounding/reverse causation

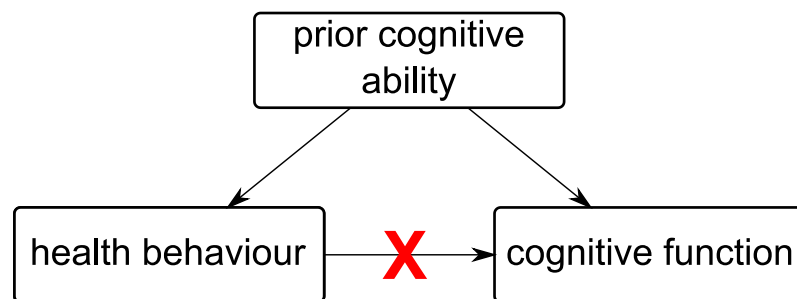


Figure 1. Two different hypotheses representing the relationship between health behaviours and cognitive function in later-life

3.4 Socioeconomic Status, IQ and lifestyle

As the powerful influence of childhood IQ on adult lifestyle, health and cognition is discussed, so too should the role of socioeconomic factors. A substantial body of literature (in psychology, epidemiology, public health and medicine) suggests that socioeconomic status (SES) is associated with both physical and cognitive outcomes in adulthood. Those of lower SES tend to be particularly vulnerable to health risks throughout their lifetimes (Lee, Back, Kim, & Byeon, 2010). In terms of health management, people with lower SES are less likely to adhere to healthy behaviours (Laaksonen, Prättälä, Helasoja, Uutela, & Lahelma, 2003), have differential access to health services, and are less likely to visit a GP (Acheson, 1998). Population-wide health

promotion campaigns have been shown to reach high SES groups first, and only later, filter to those at the lower end of the SES scale (Victora, Vaughan, Barros, Silva, & Tomasi, 2000). People with the highest social class markers of adversity tend to perform less well on cognitive assessments (Long, Ickovics, Gill, & Horowitz, 2001), and several studies suggest an aggregate or cumulative effect of socioeconomic risks, including childhood socioeconomic conditions, education, income, occupation, and wealth, on cognitive impairment (Lee, Back, Kim, & Byeon, 2010; Long et al., 2001; Zhang, Gu, & Hayward, 2008). Several studies have demonstrated an effect of early-life socioeconomic adversity on late-life cognitive function independently of adult socioeconomic status (e.g. Zhang et al., 2008). More recent research suggests that adult SES may act as a mediator in the relationship between childhood conditions and later-life cognitive function such that adult socioeconomic achievement may reverse adverse effects of childhood socioeconomic conditions and thus afford cognitive protection (González, Tarraf, Bowen, Johnson-Jennings, & Fisher, 2013). Thus, socioeconomic status is a life-course phenomenon, with different socioeconomic indicators influencing cognitive health differently at different stages (Fors, Lennartsson, & Lundberg, 2009; González et al., 2013; Lee, Back, Kim, & Byeon, 2010). Early-life factors such as education and later-life risks such as income might influence cognitive health trajectories through different pathways (Lee, Back, Kim, & Byeon, 2010).

IQ and SES are intricately linked throughout the life course and are correlated predictors of health outcomes. Higher childhood cognitive ability scores in childhood predict advantageous social circumstances in adulthood including occupational and financial attainment and a higher SES (Deary et al., 2005). The complex association between IQ and SES is an example of a complex set of gene and environment contributions and relationships. There is some evidence, for instance, that, in childhood, genetic influences on IQ are stronger in higher SES environments than in more deprived environments (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003), possibly indicating that some genes involved in IQ tend to be expressed only in higher SES settings. Alternatively, it may mean that there is more overall variance at lower SESs with greater environmental contribution. IQ and SES are generally moderately correlated, suggesting that IQ can influence an individual's SES and/or vice versa. Furthermore, parents pass on genes for both intelligence and socioeconomic environment to their children (Deary, Penke et al., 2010; Marioni et al., 2014). Using DNA SNP data from nearly 7000 subjects in the Generation Scotland study, Marioni et

al. (2014) observed a genetic contribution to variation in SES, 26% of which was shared with the genes that influence intelligence. The implication of these analyses is that SES has, in part, genetic causes that are shared with the genetic contributions to measured intelligence.

Although there are clear SES gradients in lifestyle factors such as smoking, diet, physical activity and obesity (Darmon & Drewnoski, 2008; Gidlow, Johnston, Crone, Ellis, & James, 2006; Schaap, van Agt, & Kunst., 2008), there are several suggestions in the literature that IQ is the primary influence, and that SES mediates its effect (Hagger-Johnson, Mõttus, Craig, Starr, & Deary, 2012; Batty, Deary, & Gottfredson, 2007). Many of the reported associations between childhood IQ and smoking, vascular morbidities, and the metabolic syndrome, were significant after adjustment for social class (see Kilgour, Starr, & Whalley, 2010) suggesting that a role for childhood IQ remained. Previous work on the LBC1936 found that educational attainment and social position contributed only small independent effects to late life cognitive ability once prior cognitive ability was accounted for (Johnson et al., 2010). Without a measure of prior cognitive ability the advantages of education or social class in terms of cognitive outcomes can be overstated. As previously mentioned, these factors are themselves predicted by earlier cognitive ability (Deary et al, 2005; Gow et al, 2011; Johnson, Deary, McGue, & Christensen, 2009). That SES has an independent effect is not in question, but it is likely that it contributes a small amount of independent variance in later ability level, once IQ/cognitive ability in youth is taken into account.

3.5 Summary

Lifestyle-related risk factors for cognitive ageing and dementia have been studied extensively in the last decade. In general, the studies examining the associations between lifestyle and cognitive function, to date, indicate that there may be a relationship between health behaviours and individual differences in cognitive functioning. The implication is that engaging in a healthy lifestyle may buffer the decline in cognitive abilities typically experienced with age. The purpose of this thesis is to address some of the methodological concerns in the current literature, including the possibility of confounding and reverse causation by prior cognitive ability, which are often not even acknowledged. In doing so, the current thesis represents a necessary set of analyses which may help to shed light on the nature of the lifestyle-cognitive function associations in later-life.

PART II: METHODS

Chapter 4 - Methodology

4.1 General aims and approach

The overall aim of this thesis is to identify possible associations between lifestyle factors and cognitive function in a cohort of relatively healthy, community dwelling older individuals. Associations are examined from an epidemiological perspective using a series of observational studies. Each lifestyle factor is examined independently. Each of the studies in the thesis specifically address the role of childhood IQ primarily, and SES, in the relationships between lifestyle and cognitive function in older age. The body of work represented in this thesis is based on a series of six published, peer-reviewed first-author articles, and one co-authored article, examining the association between lifestyle, and lifestyle-related factors, and cognitive functions, in the Lothian Birth Cohort 1936 (LBC1936) Study. As previously noted, studies that can account for the stability of cognitive abilities are rare. This is a sample, described below, for whom valid intelligence records from youth are available, permitting evaluation of a possible link between childhood IQ, lifestyle and cognitive function in later-life, and making it ideally suited to addressing the aforementioned issues. This early measure of intelligence provides a significant advantage over previous research, which typically only estimates prior IQ, or assesses cognitive ability at baseline in older age.

4.2 Dataset: the Lothian Birth Cohort 1936 (LBC1936)

The Lothian Birth Cohort 1936 (N=1091, see Figure 2) is a sample of men and women born in 1936, most of whom have intelligence test scores available from age 11 years. On 4 June 1947, almost all children in Scotland born in 1936 (n = 70,805) took a version of the Moray House Test (MHT) Number 12 as part of the Scottish Mental Survey of 1947 (SMS, 1947; see Deary, Whalley, & Starr, 2009). The MHT is a group-administered test of general intelligence, concurrently validated ($r \sim 0.8$) against the Terman–Merill revision of the Binet scales (Scottish Council for Research in Education, 1949). The SMS1947 was an almost complete population assessment of people born in 1936. Participants in Edinburgh and its immediate surrounding area (Lothian) were traced in later-life, almost 60 years later, and invited to take part in a longitudinal study

of cognitive ageing, known as the Lothian Birth Cohort 1936 (Deary et al., 2007). This was achieved by using the Community Health Index, and latterly, media advertisements. The participants were invited to attend for detailed cognitive, medical and other testing, and questionnaire assessment, between 2004 and 2007, at a mean age of about 70 years. In total, 1091 relatively healthy participants (548 men and 543 women) were recruited and tested individually at the Wellcome Trust Clinical Research Facility at Western General Hospital, Edinburgh. The mean age of the LBC1936 when tested as children in the SMS1947 was 10.9 years old (SD = 0.3) and the first follow-up in older age was conducted at a mean age of 69.5 years old (SD = 0.8). These will be referred to as age 11 and age 70 throughout this thesis.

The LBC1936 participants were asked to complete a battery of cognitive tests administered by trained psychology research assistants, undergo a physical examination with a research nurse, and provide demographic and other psychosocial lifestyle information. Dietary intake was recorded using a food frequency questionnaire (FFQ), described below. Only the variables relevant to the current thesis are described in the following sections; an overview of the full assessment is given in Deary et al. (2007).

As this cohort provides data about cognitive ability in early-life as well as older age, it offers a rare opportunity to study lifetime cognitive change. In terms of this thesis, this enables an assessment of the variance explained by lifestyle factors once early-life (premorbid) cognitive ability is accounted for.

4.3 The seven lifestyle factors examined

In the thesis I discuss findings from seven studies, in the context of the existing literature, and evaluate the contribution of these studies to the advancement of knowledge of cognitive ageing. The cross-sectional associations are reported between seven aspects of lifestyle identified in the previous literature as potentially important predictors of cognitive performance. Diet, alcohol consumption, smoking, and physical activity are often referred to as 'the big four', and have been the focus of recent research efforts and their relationship with cognition is well-documented in literature. In addition to the big four, caffeine consumption, body mass index, and serum cholesterol levels are investigated. These multiple factors have not before been studied in the same cohort.

The first three studies focus on dietary intake, specifically: caffeine consumption (Corley, Jia et al., 2010); alcohol consumption (Corley et al., 2011), and; dietary patterns (Corley, Starr, McNeill, & Deary, 2013). Dietary factors such as coffee consumption, moderate alcohol consumption and a Mediterranean-style dietary pattern have all been implicated in successful ageing. The fourth study addresses the relationship between body mass index and cognitive performance (Corley, Gow, Starr, & Deary, 2010). Body mass index is an important predictor of health and a potential predictor of cognitive function, and closely related to other lifestyle factors such as dietary intake and physical activity. A fifth study evaluates the much-cited association between smoking behaviour and poor cognitive function (Corley, Gow, Starr, & Deary, 2012). The sixth study investigates the complex association between serum cholesterol measures and cognitive function (Corley, Starr, & Deary, 2015). An additional article, on which I am a co-author, and on which I made a substantial contribution (in terms of data collection, statistical analysis, and contributing to the writing) is summarised as it is valuable to the coherence of this thesis; physical activity is considered to be one of the main lifestyle factors to have a positive benefit for cognitive ageing. This article (Gow, Corley, Starr, & Deary, 2012) examines the association between physical activity and cognitive function using the same design and statistical methodology adopted in the previous papers by Corley and colleagues.

Specifically, the thesis tests the hypotheses that the previously reported associations between a high caffeine intake, a moderate alcohol intake, a healthy dietary pattern, a lower BMI, smoking avoidance, a higher total and high-density lipoprotein (HDL) cholesterol level, and increased physical activity, may be substantially confounded by higher prior cognitive ability and, by association, SES. Each peer-reviewed article contains a review of the relevant literature and a discussion of how the findings contribute to the literature on potential determinants of cognitive ageing. Part III reflects on the studies presented in this thesis by evaluating the findings from a broader perspective, within the framework of the current literature, and discussing methodological considerations, practical implications and directions for future research.

Chapter 5 - Measurement of Cognitive Function

5.1 The psychometric approach

Individual differences in intelligence are usually measured using psychometric tests; cognitive measures can only be inferred indirectly by assessing performance on tasks that are assumed to represent these abilities (Salthouse, 2010a). The terms cognitive abilities, intelligence, IQ, psychometric intelligence, mental abilities, and cognitive functions, are often used interchangeably (Deary & Batty, 2007). Throughout this thesis, these terms all refer to psychometric intelligence, as measured by standardised mental tests. A broad definition of intelligence has been proposed by a group of prominent researchers in the field:

“Intelligence is a very general capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill or test-taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings—‘catching on’, ‘making sense’ of things, or ‘figuring out’ what to do. Intelligence, so defined, can be measured, and intelligence tests measure it well.” (Gottfredson, 1997a).

Individual differences in human intelligence are among the most robust observations in psychology (Deary, Penke et al., 2010). The frequently controversial history of psychometrics spans over 100 years. Over this time, a number of theoretical concepts have been put forward to account for these differences, generating much debate over the last century among those in the fields of psychology and epidemiology. Central to this were two contrasting suggestions: that individual’s scores on multiple tests of cognitive ability were correlated and best represented by general cognitive ability (Spearman, 1904), and that cognitive ability differences were best represented by a number of separate cognitive domains (Thurstone, 1936).

5.1.1 Psychometric tests and *g* – common variance

Psychometric tests take account of cognitive domains such as reasoning, executive function, memory, processing speed and spatial ability. Although cognitive domains have traditionally been considered to be independent, the field of differential psychology has unequivocally found that they are not (Carroll, 1993). Individuals who perform well in one domain, on average, tend to perform well in others. The term ‘general intelligence’, referred to as *g*, is commonly used to reflect general cognitive ability, proposed first by Spearman (1904), which is applicable to any kind of cognitive

problem. General intelligence is important as it accounts for much of the predictive validity of cognitive tests. All intelligence tests, regardless of whether they are unitary or more complex multifaceted tasks, are correlated and tend to produce a strong general factor when applied to a large sample of people. In typical test batteries comprising upwards of ten different cognitive tests involving various materials and content, a *g* factor almost always accounts for around 40% or more of the total variance (Deary, 2012a; Deary, Penke et al., 2010; Harris & Deary, 2011; Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004; Johnson, te Nijenhuis, & Bouchard, 2008; Plomin & Spinath, 2002). Likewise, the terms cognitive ability, mental ability, intelligence and IQ, represent the strong common core that cognitive tests share.

Typically, *g* is the first unrotated principal component (or factor) from a battery of mental tests administered to a sample of a population. It describes the near-universal finding that all mental tests tend to correlate positively (Carroll, 1993). The *g* extracted from different, large mental test batteries correlates at levels that are above $r = 0.9$. (Johnson et al., 2004).

General intelligence differences are associated with important life outcomes including school and occupational achievement, job performance, and social mobility (Strenze, 2007; Gottfredson, 1997b). People with higher general intelligence in youth have better health in middle and later-life and are less likely to die young (Calvin et al., 2011). Intelligence in early adulthood and middle age predicts risk of premature mortality as strongly, or better than, other commonly assessed risk factors including blood pressure, dyslipidaemia and body mass index (Batty, Shipley, Gale, Mortensen & Deary, 2008).

In recent years, validity for psychometric intelligence measures is provided by data from brain imaging and genetic studies, which show strong correlates with results from intelligence tests. General intelligence differences are substantially heritable (Deary, Johnson, & Houlihan, 2009; Deary, Penke et al., 2010), and general intelligence and brain size and efficiency show modest, positive correlations (McDaniel, 2005). Although these findings demonstrate correlations and not causal mechanisms, these two areas represent the most promising avenues for studying the neuroscience of general intelligence in the future. Further discussion of this interesting and evolving area is beyond the remit of this thesis, but given their broad consideration in cognitive

research today, several genetic and brain imaging studies are cited in the discussion in Part 3.

5.1.2 Psychometric tests and specific variance

Apart from the shared variance, each individual cognitive test also shows a substantial amount of specific variance, generally ranging from 20% to 50% of the total variance (Deary, 2001). This reflects the particular abilities involved in that test. Some of this can be attributed to error variance or variance resulting from person-specific factors affecting performance such as fatigue or mood factors. Various tests requiring certain broad abilities such as word knowledge or spatial awareness, tend to be highly correlated as individuals often have areas of strengths or indeed weaknesses. However, much less variance is contained within broad domains of capability (Deary, Penke et al., 2010).

Haier et al. (2009) explained that participants' scores result from *g*, cognitive abilities (group factors), and cognitive skills (test specificities). Group factors representing specific abilities also represent an important level of analysis (Plomin & Spinath, 2002). There is a growing consensus that it is valid to examine both general and specific cognitive abilities (Deary, 2001; Harris & Deary, 2011). Just as factor analysis is used to extract a *g* factor from psychometric tests, factors representing major cognitive domains such as memory and processing speed can be derived from a large number of cognitive tests (see Deary, Penke et al., 2010).

5.1.3 Fluid and crystallised intelligence

The theory of fluid and crystallised intelligence was developed by Cattell & Horn to distinguish between two aspects of *g* (Horn, 1989). Fluid intelligence is considered to be our basic information-processing capability, which is best captured using tests of novel material under time pressure. Abilities such as speed of processing, memory, spatial ability, and reasoning are fluid abilities and tend to decline with age. Crystallised intelligence represents the stored knowledge acquired over time, which is best captured by tests like vocabulary and other knowledge-based assessments. Although they are highly correlated, there is a marked difference in the way they change with age (Craik & Bialystok, 2006). Fluid intelligence declines like other physical abilities whereas crystallised intelligence, such as word knowledge (captured in tests such as the NART), shows little age-related cognitive decline. In fact, vocabulary is preserved even

during the initial stages of dementia, at a time when fluid intelligence has declined markedly (McGurn et al., 2004). Given that there are distinct ageing patterns for fluid and crystallised intelligence, it is important that they are examined independently.

5.1.4 Processing speed

Attempts to explain differences in intelligence and cognitive ageing are often founded substantially upon differences in speed of information processing (Salthouse, 1996). That more intelligent people react to and inspect visual and auditory stimuli more rapidly than less intelligent people is a well-established finding (Deary & Stough, 1996; Deary, Penke et al., 2010; Ritchie, Tucker-Drob, & Deary, 2014). People with higher intelligence have faster and less variable reaction times, for example (Deary, Der, & Ford, 2001). Functional neuroimaging studies are generally consistent with the hypothesis that more intelligent brains process information more efficiently, i.e. use fewer brain resources, than less intelligent brains (Haier et al., 1988; Deary, 2000). One study found there was no longer a significant association between intelligence and mortality following adjustment for individuals' reaction times (Deary & Der, 2005). This finding is crucial as it might be seen as evidence for the theory of general body (system) integrity (of which faster reaction times is a marker) underlying both intelligence and mortality. This theory will be revisited in Part III.

Studies typically use conventional processing speed tests such as Digit-Symbol Substitution and Symbol Search, both paper and pencil tests, or reaction time tasks. These tests are useful measures of processing speed and decision response speed, but at the same time, they rely upon other mental processes such as memory or reasoning and physical reactions such as motor speed that may be subject to decline with age for entirely non-cognitive reasons. Free from these constraints, because it needs no speeded motor response, is a visual inspection time task which is a psychophysical indicator of the efficiency of early-stage perceptual processing. Using this task, Ritchie et al. (2014) found strongly coupled changes in intelligence and inspection time over time, similar in magnitude to performance on the more conventional processing speed measures. These findings not only confirm that level of basic processing speed correlates with level of intelligence, as found in previous work (e.g. Deary & Stough, 1996; Nettelbeck, 2011) but that cognitive change is accompanied by changes in basic (lower-level) visual information processing as we age, supporting the processing speed

theory of ageing. In terms of cognitive ageing research, Inspection Time may serve as an early biomarker of age-related decline (Deary, Johnson & Starr, 2010)

The above discussion sets the ground for the following sections which describe the tests used in the LBC1936 cognitive battery and supports the use of a general cognitive factor g , as well as specific major age-related cognitive domains—processing speed, memory, and crystallised ability, and aid in the interpretation of the findings from each analysis.

5.2 The LBC1936 cognitive test battery

All participants were administered a comprehensive battery of psychometric/neuropsychological tests to assess cognitive function, based largely on the Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III; Wechsler, D, 1998a) and the Wechsler Memory Scale-III^{UK} (WMS-III; Wechsler, 1998b). Scoring of all tests was performed by trained psychologists. A description of each test follows.

5.2.1 The cognitive tests

The Mini-Mental State Examination (MMSE) was administered as a standardised first-stage screening measure for cognitive pathology (Folstein, Folstein, & McHugh, 1975). It is commonly used as a brief screening test for dementia consisting of 30 questions that assess orientation to time and place, short and delayed memory recall, registration, constructional ability, language, and the ability to understand instructions. Scores range from 0 to 30, with a score of less than 24 generally accepted as an indicator of possible dementia (Lezak et al., 2004). Those scoring below the cut-off were excluded from the analyses, as is standard in studies of normal cognitive ageing.

Moray House Test (MHT) Number 12. The participants in the LBC1936 had mostly taken part in the nationwide SMS1947. The Moray House Test Number 12 was one of a number in this series used (Scottish Council for Research in Education, 1949) for the purposes of selection from primary to secondary education. It is a paper and pencil group administered test, which has a 45-minute time limit. The MHT was devised by Godfrey Thomson, Principal of Moray House College of Education in Edinburgh (Thomson, 1940). This ‘verbal reasoning’ test has 71 numbered items, 75 questions in total, of a variety of types: following directions (14 items); same-opposites (11 items); word classification (10 items); analogies (8); practical items (6); reasoning (5); proverbs (4); arithmetic (4); spatial items (4); mixed sentences (3); cypher

decoding (2); and other items (4). The maximum possible score in the Moray House Test (MHT) is 76.

The MHT was validated in a sub-sample of 1000 children (500 boys and 500 girls) drawn from the Scottish Mental Survey of 1932 (Scottish Council for Research in Education, 1933). This group completed the Stanford revision of the Binet-Simon Test (as standardised by Terman). Correlations between the MHT and Binet IQ test were 0.8 (for boys) and 0.76 (for girls), providing concurrent validity for the MHT (Deary, Whalley et al., 2009; Scottish Council for Research in Education, 1933). The MHT was readministered to LBC1936 participants at age 70. The same instructions and 45-minute time limit were used. MHT scores at age 11 and age 70 were corrected for age in days at time of testing and converted into IQ-type scores for the sample ($M = 100$, $SD = 15$).

The Wechsler Adult Intelligence Scale-III (WAIS-III^{UK}, Wechsler, 1998a) and the *Wechsler Memory Scale* (WMS-III^{UK}, 1998b). The WAIS is one of the most widely used sets of cognitive test batteries to assess intelligence. They are administered by a trained tester to an individual subject. A validation study, based on 2450 adults in the US, demonstrated a mean correlation among the various (thirteen) tests of different domains of thinking in the WAIS-III, to be 0.49 (range 0.26-0.77). In essence, those performing well on one test tended to do so on the others, and vice versa. The reliability of this battery of tests is high. The mean test-retest reliability of these tests was 0.85 (range 0.77-0.93). Four identifiable cognitive domains underlie these tests, namely: verbal comprehension, perceptual organisation, processing speed and working memory (Wechsler, 1997). The Wechsler Memory Scale (WMS-III) is a neuropsychological test designed to measure different memory function, namely, immediate memory, general (delayed memory), and working memory.

The LBC1936 psychometric test battery was chosen to provide a comprehensive assessment of cognitive function (Deary et al., 2007). Participants took six subtests from the Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III; Wechsler, 1998a), namely: Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; Symbol Search. Participants took subtests from the Wechsler Memory Scale-III^{UK} (WMS-III; Wechsler, 1998b), namely: Logical Memory I immediate and II delayed recall; Spatial Span Forwards and Spatial Span Backwards; Verbal Paired Associates I immediate recall and II delayed recall.

Verbal ability was assessed using the National Adult Reading Test (NART; Nelson and Willison, 1991) and Wechsler Test of Adult Reading (WTAR; Holdnack, 2001). Both of these tests require the subject to read aloud 50 irregular words, i.e. none of which follow normal English rules of grapheme-phoneme correspondence and/or stress. These tests are widely used to estimate prior (crystallised) cognitive ability given that verbal ability is less likely to have declined with age, even in those with dementia (McGurn et al., 2004).

Reaction Time and Inspection Time. Participants also completed a simple and choice reaction time task (Cox, Huppert, & Whichelow, 1993; Deary, et al., 2001) and a computer-based visual processing speed task known as Inspection Time (Deary, Simonotto et al., 2004).

5.2.2 Data reduction: *g*, processing speed and memory factors

From the individual tests, composite cognitive function scores were extracted using principal components analysis to represent three major ageing-related cognitive domains: general cognitive ability (*g*), processing speed (Luciano, Gow, et al., 2009) and memory (Corley, Jia et al., 2010). Regression scores were calculated for the first unrotated principal component. The amount of variance accounted for in these derived factors is almost exactly as is usual (Carroll, 1993) in this type of work, and is substantial.

- (1) A general cognitive ability (often referred to as *g*) factor, was derived from scores on the WAIS-III subtests: Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; Symbol Search. A general cognitive ability (*g*) factor is well established in the literature (Deary, Penke et al., 2010). Inspection of the Scree slope (see Figure 3.1), and the Eigenvalues-greater-than-one criterion, indicated a single component, which accounted for 53% of the variance. Each individual test was found to load strongly on *g* [range 0.66–0.77]. Individuals' scores on the first unrotated principal component were used to represent general cognitive ability.
- (2) A processing speed factor was derived from scores on a set of mental processing speed measures, namely: Symbol Search; Digit Symbol; Simple and Choice Reaction Time mean; Inspection Time. Inspection of the scree slope (see Figure 3.2), and the Eigenvalues-greater-than-one criterion, indicated a single component, which accounted for 51% of the variance. Each individual test was

found to load strongly on the speed factor [range 0.60–0.79]. Individuals' scores on the first unrotated principal component were used to represent processing speed.

- (3) A memory factor was derived from scores on a set of memory measures namely: Logical Memory I immediate and II delayed recall; Spatial Span Forwards and Spatial Span Backwards; Verbal Paired Associates I immediate recall and II delayed recall; Letter-Number Sequencing, Digit Span Backwards. Inspection of the scree slope (see Figure 3.3), and the Eigenvalues-greater-than-one criterion, indicated a single component, which accounted for 43% of the variance. Each individual test was found to load strongly on the memory factor [range 0.48–0.78]. Individuals' scores on the first unrotated principal component were used to represent memory.

Chapter 6 - Measurement of Lifestyle Factors and Other Variables

6.1 Dietary consumption

Maintaining a healthy nutritional status in later-life is problematic due to factors such as loss of appetite, a decline in income, access to shops and cooking facilities, and disease states. Many older people are deficient in micronutrients (Finch et al., 1998). Age itself is a moderating factor in how certain food related factors, such as variety, influence eating behaviour (Remick, Polivy & Pliner, 2009).

Researchers face challenges in nutritional assessment in older people as a result of hearing, mobility, and eyesight loss. Consequently, there is a body of research which has focussed on developing appropriate tools suitable for the assessment of dietary intake in this age group. Dietary assessment methods that rely on short-term memory or lengthy interviews, such as the 24-hour recall and diet history methods, have limitations for those in older age. The food frequency questionnaire (FFQ) does not rely on short-term memory and has been found to be suitable for those with stable dietary habits (Lazarus, Wilson, Gliksman, & Aiken, 1995). Asking respondents to recall food items frequently consumed may be less of a challenge than recalling specific food items, as in the 24-hour recall method.

6.1.1 The Food Frequency Questionnaire (FFQ)

Caffeine (Corley, Jia et al., 2010), alcohol (Corley et al., 2011) and dietary (Corley et al., 2013) data were derived from responses to a self-report food-frequency questionnaire (Scottish Collaborative Group (SCG) FFQ version 7.0; see <http://www.foodfrequency.org>). The SCG FFQ is a research instrument designed to estimate daily intake of a wide range of nutrients in large scale epidemiological studies in adults in the UK. It has been developed in Aberdeen, Dundee and Cambridge from the diet questionnaire used in the Scottish Heart Health Study and MONICA study. It is designed to estimate habitual diet over the previous 2-3 months (or other specified period) and was completed by the participants at home using a paper copy. It includes up to 175 commonly-eaten types of food or drink grouped into 19 sections and is semi-quantitative, i.e. respondents estimate the amount of each food they have as well as how often they have it. For each item, participants mark one of nine responses to indicate frequency of consumption ranging from rarely or never to 7+ times per day.

The FFQ (Masson et al., 2003) has good repeatability (dietary intake is reasonably stable in the short term) and good validity, compared with 4-day weighed diet diaries, for most nutrients in community-dwelling older populations (Jia, Craig, Aucott, Milne, & McNeill, 2008; McNeill, Winter, & Jia, 2009). McNeill et al. (2009) found little evidence that cognitive function in older age influences validity.

6.2 Measuring the other lifestyle factors

The other lifestyle factors were assessed using standard measurement tools; further details can be found in the relevant papers. In brief: physical activity level was assessed via a questionnaire completed at home and returned at the clinic appointment (Gow, Corley et al., 2012); body mass index data is derived from height and weight measures obtained at the physical examination (Corley, Gow et al., 2010); smoking behaviour data is derived from responses given during the health and medical history interview (Corley et al., 2012); and, serum cholesterol was derived from results of a blood profile taken as part of the medical assessment (Corley et al., 2015).

6.3 Measuring the demographic, health, and other variables

Important variables that could potentially confound any association between health behaviours and cognitive function, apart from prior IQ, are socioeconomic status and physical health. These factors were included as covariates throughout the studies, wherever relevant. Socioeconomic status was represented by occupational social class, derived from participants' highest reported occupation (Office of Population Censuses and Surveys, 1980), and consisted of six categories ranging from I (professional occupations) to V (unskilled occupations), with III (skilled occupations) divided into IIIN (non-manual) and IIIM (manual). Married women were asked to provide a description of their husband's occupation and assigned a social class category based on the highest occupation of the household. Participants also provided the number of years in full-time education. A medical history was taken during LBC1936 clinic visits including history of hypertension, diabetes, cardiovascular disease, stroke, hypercholesterolemia, and current medications.

6.4 Statistical Methods

All analyses were conducted in PASW Statistics version 17.0, 18.0, or 19.0. Each study used analysis of variance (ANOVA) and chi-square tests to firstly examine whether demographic and health variables differed between categories of the lifestyle factor

being studied. For the main analyses, each lifestyle factor was entered into general linear models (ANCOVA) as a continuous predictor variable. Cognitive outcomes (dependent variables) were age 70 (MHT) IQ, general cognitive ability (*g*), processing speed, memory, and verbal ability (NART and WTAR). Using a general linear model approach for each set of analyses allowed us to control for potentially confounding variables, including, age, sex, childhood cognitive ability (IQ), and adult occupational social class. Even though our sample shared the same year of birth (1936), assessment took place over a three year period (2004 to 2007). The age range at time of assessment in the current sample was 67.6 -71.3 years (mean = 69.5, SD = .83). Although this is a relatively small difference, we always adjusted for the effects of chronological age when examining cognitive outcomes. Additional potential confounding variables were included in the analyses if relevant. Relevant estimates of effect size are presented, reported as partial eta-square (η_p^2), and p-values are also given (the 0.05 level of significance was used for all data analyses with the appropriate discussion of possible type 1 errors). In examining any attenuation by covariates, attention is drawn to the change in effect size, not merely to any change in the significance level.

PART III: DISCUSSION

Chapter 7 - Results and General Discussion

7.1 Study objectives revisited

The objectives of the present thesis were to investigate lifestyle determinants of cognitive functioning in older community dwelling adults, free from dementia. A series of cross-sectional studies considered a number of lifestyle factors which have been proposed as cognitively protective. Part I discussed the potential lifestyle-cognition relationships based on previous literature and provided a rationale for the influence of lifetime stable 'trait' IQ on these observed associations. The possibility of reverse causation is central to this thesis. The possibility that the associations between better lifestyle habits and improved cognitive performance might be wholly or partly attributable to prior cognitive ability predicting both, has implications for cognitive ageing research. Thus, the primary objective was to identify lifestyle factors with an independent effect on cognitive function in later-life after the confounding effects of lifetime stable levels of IQ were accounted for. This chapter summarises the main findings and discusses the implications of this research, relevant methodological considerations and directions for future research.

7.2 Main findings

7.2.1 General demographic results

The LBC1936 cohort was relatively cognitively healthy, as shown by the mean MMSE obtained; $m = 28.8$ ($SD = 1.4$) out of a maximum of 30. At age 70, 11 participants scored less than 24 on the MMSE (often used as an indicator of possible dementia), and no participant scored below 20. They had a mean of 10.7 years ($SD = 1.1$) of full-time formal education, a mean weekly alcohol consumption of 10.5 units ($SD = 14.2$), and a mean BMI of 27.8 ($SD = 4.3$). 11.5% were current smokers, 42.6% were ex-smokers and 45.9% were never smokers. The majority of participants were grouped in social classes 1-3; 17.8% participants were in social class 1 (the highest grouping), 37.6% were in social class 2, 23% were in social class 3 (non-manual) and 17.6% in social class 3 (manual). Social classes 4 and 5 consisted of 3.5% and 0.6% of participants,

respectively. The raw MHT score (out of a maximum 76) for participants at age 11 was 49.0 (SD = 11.8) and 64.2 (SD = 8.8) at age 70. Comparing performance on the MHT at age 11 to age 70, the participants showed a significant improvement; the difference between average MHT scores at 11 and 70 years old for the LBC1936 was 15.2 points [49.0 vs. 64.2, $t(1016) = 56.19$, $p < .001$, Cohen's $d = 1.46$].

7.2.2 Stability of the Moray House Test (MHT)

Correlating MHT performance across several decades provides an indication of its stability. The stability coefficient across nearly 60 years (11 to 70 years old) was 0.69 ($p < 0.01$, $N = 1017$). This finding demonstrates the high stability in cognitive ability across several decades of the human life course. The cumulative evidence suggests that about 50% of the variance in later-life cognitive ability test performance is accounted for by childhood cognitive ability. The stability of cognitive ability over long periods of time is now well-established, especially in the cohorts derived from participants of the SMS surveys, namely, the Aberdeen Birth Cohort 1936 (ABC1936; Deary, Whiteman et al., 2004), the Lothian Birth Cohort 1921 (LBC1921) and the LBC1936 (Deary, Gow et al., 2011; Deary, Whalley et al., 2009; Deary, Whiteman et al., 2004; Gow et al., 2011), as well as other longitudinal studies such as the Nun Study (Riley, Snowdon, Desrosiers, & Markesbery, 2005).

7.2.3 Childhood IQ: a major confounder

Whereas the finding that IQ levels demonstrate stability across the lifetime in this cohort is not novel, it is prescient when considering other determinants of the level of cognitive ability in later-life. The findings are interesting, partly as a result of the overwhelming generalities which appeared across this series of seven studies. The initial results (adjusted for age and gender) of each paper were broadly in accordance with previous research which identified these lifestyle and lifestyle-related factors as potentially cognitively protective. In general, better cognitive function at age 70 was associated with a higher caffeine (especially coffee) intake (Corley, Jia et al., 2010), a higher alcohol (especially wine) intake (Corley et al., 2011), a Mediterranean-type dietary pattern (Corley et al., 2013), maintaining a 'normal' body mass index (Corley, Gow et al., 2010), smoking avoidance (Corley et al., 2012), physical activity (Gow, Corley et al., 2012) and a 'healthy' later-life lipid profile (Corley et al., 2015). These seemingly beneficial associations held across the cognitive domains tested: general

(fluid) cognitive ability (*g*); processing speed; memory; and verbal (crystallised) ability and suggested that these factors account for around 1% of the variance in cognitive performance. These preliminary findings are in accordance with those of many previous studies and support the theory that a healthy lifestyle may 'buffer' the effects of cognitive ageing.

However, further analyses demonstrated that these lifestyle factors (caffeine consumption; alcohol consumption; diet; body mass index; smoking; physical activity; and cholesterol) did not exhibit robust or straightforward relationships, if any, with cognitive performance in later-life. When statistical models that included a direct, validated measure of childhood IQ, and to a lesser extent adult SES (based on highest achieved adult occupational-based class), were tested, most of the 'protective' effects of these factors on cognitive function were removed, or at the least, markedly attenuated, often by around 50-80%. For example, after controlling for the effects of prior IQ and SES, a higher caffeine intake was found to be neither beneficial nor detrimental to performance on cognitive tests. Instead, those who drank more caffeine, and more ground coffee in particular, were more likely to have a higher IQ in childhood and older age (Corley, Jia et al., 2010). Likewise, the association of a higher alcohol intake and better cognitive abilities (age 70 IQ, *g*, and processing speed) could be explained by those with a higher prior cognitive ability in youth, drinking more alcohol years later, and also having a preference for wine consumption over other types of alcohol (Corley et al., 2011). A higher BMI, indicative of being overweight or obese, was associated with poorer cognitive performance at age 70, but this could largely be accounted for by lower lifetime IQ and SES (Corley, Gow et al., 2010). The same held true for diet; the well-established finding of better cognitive performance in those adhering to a Mediterranean diet rather than a conventional diet could be explained by a higher IQ in youth and SES in adulthood (Corley et al., 2013). When the lipid profile of participants were tested in the serum cholesterol analyses (Corley et al., 2015), all the significant effects of cholesterol (higher total-, higher HDL-cholesterol, and lower triglycerides) with better cognitive function were removed. At the same time as noting commonalities, there were obvious exceptions, which are discussed below.

7.2.4 Which lifestyle factors might contribute to healthy cognitive ageing?

Alcohol consumption, smoking, and physical activity were the three lifestyle factors measured which were found to make an independent contribution to cognitive performance in older age once the effects of prior IQ and adult SES were removed. These findings are discussed in brief below.

Alcohol

Although there was no longer an association of better cognitive function with overall alcohol intake in units with age 70 IQ, *g*, and processing speed, an independent association was observed between a higher alcohol (particularly wine) consumption and better memory function and verbal ability (in women only) at age 70 (Corley et al., 2011), accounting for around 1% in women and 1.2% in men, of the variance in scores. As the women's intake derived almost completely from wine, this was suggested to be a potentially beneficial effect of wine. However, memory performance was better in men with a higher overall alcohol intake and not necessarily due to wine intake per se. Thus, regular consumption of wine (equivalent to one glass of wine per day or more) in the LBC1936, was found to make a small, positive contribution to one domain of cognitive performance—memory—in later-life, but not to *g*, processing speed, or age 70 MHT IQ. As noted in the paper, wine drinkers tend to have more favourable health and lifestyle characteristics, such as a healthier diet, than consumers of beer and spirits. However, there may be biological mechanisms underlying a link between wine consumption, especially red wine, and better cognitive function. Red wine consumption has been found to attenuate A β neuropathology associated with AD in mice (Wang et al., 2006). Red wine is also a source of polyphenols, which exhibit cardioprotective effects in humans, and are associated with a reduced risk of age-related neurodegenerative disorders including AD (see Vauzour, Rodriguez-Mateos, Corona, Oruna-Concha, & Spencer, 2010) and 10-year cognitive decline in healthy individuals (Letenneur, Proust-Lima, Le, Dartigues, & Barberger-Gateau, 2007). However, given that the positive wine intake-better memory association was robust in women, but not in men, suggests that the clinical significance of these findings is uncertain (Corley et al, 2011). The available epidemiological evidence is only suggestive of a protective effect. At present there is no indication that moderate drinking would be harmful to cognition and dementia but it has not been possible to define a beneficial level of alcohol intake (Panza et al. 2009).

Smoking

The study examining the associations between smoking (current status and amount of lifetime smoking) and cognitive performance at age 70, suggests that cognitive abilities and smoking behaviour are linked across the life course (Corley et al., 2012). Lower IQ in childhood was associated with a higher risk of becoming a smoker and of continuing to smoke in later-life. In later-life, those who were current smokers at age 70 performed more poorly than ex-smokers and never smokers on tests of *g* and processing speed independently of childhood IQ and SES. Thus, current smoking was found to make a small, negative contribution to cognitive performance in later-life, explaining 0.7% and 0.6% of the variance in *g* and processing speed performance respectively. In the LBC1936, the findings suggest that continuing to smoke in older age contributes to age-related cognitive impairments in fluid cognitive abilities (represented by *g*) and speed of information processing. Interestingly, past smoking was not associated with significantly poorer performance than never smokers in any cognitive domain, consistent with previous studies (e.g. Deary et al., 2003). Likewise, a meta-analysis of prospective studies found that compared with non-smokers, current smokers had higher rates of cognitive decline and increased risk of dementia; however, former smokers did not have an increased risk of dementia compared with non-smokers (Anstey et al., 2007).

That smoking in old-age increases the risk of cognitive impairment and AD is well-documented, but it appears to have deleterious consequences for lifetime cognitive change in healthy individuals (Deary et al., 2003; Whalley et al., 2005). Furthermore, current smoking into older age was identified as the single most consistent vascular risk associated with cognitive decline in the English Longitudinal Study of Ageing (ELSA; Dregan, Stewart & Gulliford, 2012). As noted in Chapter 2, neuroimaging studies employing MRI methods indicate that smoking may lead to both macro- and microvascular cerebral damage (Debette et al., 2011; Gons et al., 2011). However, the low rate of survival in smokers is a potential limitation of some of these studies and current smokers were under-represented in the current sample.

Cessation of smoking in adulthood may 'buffer' the cognitive ageing experienced by those who continue to smoke. Support for this hypothesis derives from a recent brain MRI imaging study. Using structural brain MRI data of around 500 of the LBC1936 participants, Karama et al. (2015) found that during the course of normal ageing, smoking accelerates cortical thinning, which is a biomarker of cognitive decline in adults. However, accounting for lifetime smoking, the cortex of subjects who stopped

smoking appeared to have partially recovered for each year without smoking. Although complete cortical recovery in affected areas took on average 25 years in this sample, these important findings suggest that partial recovery is possible. In terms of public health implications, these findings suggest that there are cognitive benefits to quitting smoking, even for older adults who have been smoking for many years; intervention programmes should target smokers at all ages. The potential to at least partially recover from smoking-related cortical thinning might serve as a strong motivational argument to encourage smoking cessation.

Physical activity

In the physical activity paper (Gow, Corley et al., 2012), participating in some physical activity (compared to being sedentary) was associated with better general cognitive ability (g) and processing speed performance. This lifestyle factor accounted for 0.7% of the variance in g and 1% of the variance in processing speed. Nevertheless, they support the compelling evidence that physical activity has a role in determining healthy cognitive ageing. Our findings are in accordance with a systematic review in 2010 (Lee, Back, Kim, Kim et al, 2010) which found that eight out of nine studies examined showed significant cognitive benefits with physical activity.

Further support for a link between physical activity and cognitive ageing comes from brain imaging studies. In a later investigation of the LBC1936 sample using structural MRI data from around 700 participants, Gow, Bastin et al. (2012) found that self-reported physical activity was associated with less brain atrophy and fewer white matter (vascular brain) lesions. This and other studies (e.g. Marks et al., 2007; Tian et al., 2014; Voss et al., 2013) suggest that being physically active may help preserve brain microstructural integrity in among community-dwelling older adults. In addition, declining physical function over a three-year period, represented by performance on typical physical function measures such as 6-metre walk, grip strength, lung function, was related to (less) brain volume at baseline in the LBC1936 sample. These associations did not diminish when covariates such as education, social class, and health status (particularly hypertension) were considered (Aribisala, Gow et al., 2013). As yet, there is a dearth of large-scale studies combining MRI assessments and long-term follow-up, so studies to date are usually limited to relatively short follow-up periods.

There are several plausible biological mechanisms underlying associations between physical activity and cognitive decline, as mentioned briefly in chapter 2.2. Physical activity reduces cardiovascular risk (Colcombe et al., 2003), increases cerebral perfusion and facilitates neurogenesis (Cotman & Engesser-Cesar, 2002; Neeper, Gómez-Pinilla, Choi, & Cotman, 1996). Exercise can help minimise and control vascular risk factors such as hypertension, hypercholesterolaemia, diabetes, heart disease and obesity (Buchner, 2009). In contrast, impaired blood flow in the midbrain is a risk factor for subsequent cognitive impairment (Zlokovic, 2011). Physical activity positively impacts physical health in other ways such as minimising pain and improving sleep (Reid et al., 2010) both of which may secondarily impact cognitive functioning, and by improving emotional health. Cognitive functioning can be adversely affected by anxiety and depression (Reppermund et al., 2011); exercise has been shown to improve mood and decrease symptoms in conditions such as depression and anxiety (Herring, Jacob, Suveg, Dishman, & O'Connor, 2012; Herring, Puetz, O'Connor, & Dishman, 2012).

There has been significant growth in the literature on exercise and cognition, with results suggesting that exercise is one of the best activities older adults can engage in to promote successful ageing and it continues to be one of the most scrutinised lifestyle factors in continuing research efforts. Across numerous studies, associations between greater engagement in physical leisure pursuits and better cognitive outcomes have been reported (Hertzog et al., 2009). Adults who are more physically active generally have higher cognitive ability, an association replicated not only cross-sectionally but longitudinally in follow-up studies spanning decades (Hultsch, Hammer, & Small, 1993, Hultsch, Hertzog, Small, & Dixon, 1999; Larson et al., 2006; Richards, Hardy, & Wadsworth, 2003; Rovio et al., 2005; Wilson, Barnes, & Bennett, 2003; Wilson, Bennett et al., 2003; Schaie, 2005a; Weuve et al., 2004; Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005; Kramer et al., 2006). A meta-analysis of prospective studies in non-demented older adults found that not only were high levels of physical activity protective against cognitive decline, but low-to-moderate activity levels were also protective (Sofi et al., 2011). Even light walking of 1.5 hours a week was found to provide some cognitive benefit (Weuve et al., 2004). This protective effect may be cumulative, as suggested by the higher cognitive performance observed among persons participating in long-term regular physical activity (Weuve et al., 2004). A persistent low level of physical activity over 11 years has previously been associated with an

increased risk of poor fluid intelligence (Singh-Manoux et al., 2005). Physical activity interventions in older adults have reported benefits for executive function, processing speed, memory and attention (Smith et al., 2010). In concordance with these findings, imaging studies also suggest that physical activity is associated with beneficial effects on brain structure including increased grey matter volume (Erikson et al., 2010) and better white matter integrity (Gow, Bastin et al., 2012; Gons et al., 2013], whereas low physical activity has been associated with increased brain atrophy (Smith et al., 2010).

7.2.5 Verbal ability and ‘peak’ intelligence

After controlling for prior IQ and SES, the only indication that some of the lifestyle factors (caffeine consumption, diet, and BMI) exerts a protective influence on cognitive performance was that those with a preference for ground coffee drinks (e.g. filter, espresso, latte and cappuccino coffee), a Mediterranean-type diet, and a BMI in the ‘normal’ category, performed better on tests of verbal ability (measured by the NART and WTAR) even after controlling for age 11 IQ and SES. Performance on these tests is widely assumed to reflect level of education. In this sample, age 11 IQ and verbal ability scores are highly correlated (NART 0.66, $p < .001$; WTAR 0.64, $p < .001$). For this reason, it was initially surprising that there remained a beneficial effect of these lifestyle factors on performance on these tests, once age 11 IQ has been controlled for. However, NART and WTAR are thought to capture peak, prior adult cognitive ability (Crawford, Deary, Starr, & Whalley, 2001; Dykiert & Deary, 2013; Richards & Sacker, 2003). These tests measure crystallised verbal knowledge, which is specifically associated with health literacy (an established marker and predictor of health inequalities), than those fluid abilities which are vulnerable to decline with age (Anstey et al., 2009). Therefore the variance in NART and WTAR does not reflect age related decline in verbal ability. Unlike initial ability, the effect of education across life is likely to be cumulative with higher or lower education predicting multiple environmental factors such as economic prosperity and occupational complexity that may directly or indirectly impact upon cognitive ageing trajectories. Perhaps the association between a more ‘cosmopolitan’ lifestyle (which includes ‘fancy’ coffee, drinking wine, and maintaining a desirable weight) and verbal ability persists, after adjusting for age 11 IQ, because vocabulary tests capture variance related to cumulative intellectual development and its associated education and life-style choices between childhood and adulthood.

It is possible that higher levels of verbal intelligence would be associated with greater general knowledge about health lifestyles, and in turn, more beneficial health behaviours. Anstey et al. (2009) found that higher levels of verbal ability were associated with higher levels of physical activity, greater likelihood of taking vitamin and mineral supplements, reduced likelihood of current smoking, and abstaining from alcohol. Studies by Wolf and colleagues have investigated the close links between health literacy and cognitive ability. They found that cognitive function explains a significant proportion of the associations between health literacy and the ability to manage one's physical health (Wolf et al., 2009). The associations between some of the lifestyle factors and verbal ability were robust in these data and the LBC1936, which suggests that the effect may be due to knowledge rather than broadly associated with more fluid type abilities. That verbal ability or verbal knowledge is more specifically associated with health literacy than fluid abilities is not surprising (Serper et al., 2014). After all, there is significant measurement overlap between some health literacy measures, such as the REALM (Davis et al., 1993), and vocabulary tests such as the NART, and both are strongly correlated (Murray, Johnson, Wolf, & Deary, 2011; Wolf et al., 2012).

In essence, it may be that peak level of cognitive ability, but not cognitive decline, is associated with health behaviour (Anstey et al., 2009). Those with higher verbal ability are more likely to engage in behaviours that are beneficial for health and that are widely recommended and adaptive such as engaging in physical activity.

7.2.6 Small effects

Given the likelihood that a large number of lifestyle or behavioural predictors will have small effects, it is inevitable that the effect sizes will be relatively small. Though small in statistical terms, such factors are still likely to be important at the population level. The most consistently cited behaviours linked to cognitive ability or ageing—smoking and physical activity (as well the variation in the *APOE* gene and inflammatory biomarkers such as C-reactive protein)—have effect sizes of the same magnitude, often accounting for 1-2% or less of the variance in cognitive outcomes (Deary, Corley et al., 2009; Deary, Yang et al., 2012; Whalley et al., 2005). Therefore, the amount of variance explained lifestyle factors may be relatively small, compared with prior cognitive ability, but small effects can have quite impressive effects at population levels. It is important to know

what these effects are, so we can discover the combination of factors that might help people age better.

7.2.7 Marginal gains: the key to healthy cognitive ageing?

In terms of preserving mental abilities or delaying cognitive decline, the available evidence suggests there is no one magic bullet. Perhaps a helpful way of thinking about successful cognitive ageing can be gained from the theory of marginal gains, a concept that has become commonplace in the world of elite sport (see Clear, 2015, <http://jamesclear.com/marginal-gains>). The principle behind the marginal gains idea is that if you improve in every variable (lifestyle factor) underpinning or influencing your performance (in our case, cognitive abilities) by just 1% or so, then, cumulatively, you get a significant improvement, or an 'aggregate of marginal gains'. It might be that it is these marginal gains or small improvements in many areas of one's life such as quitting smoking, becoming more active, eating well, sleeping well, or learning a new skill that, bit by bit, increase the odds of having a good outcome. In cognitive epidemiology, as discussed in the previous section, lifestyle factors commonly account for 1-2% or so of the variance in cognitive performance in later-life. The 'magic' may lie in the accumulation of many such gains over time to put individuals, in elite sporting terms, 'ahead of the opposition'. Insights may be gleaned from this concept and simple approach, based on a series of small healthy choices, which may not make much of a difference to one person at one time, but they might add up over the long-term. 'Good' cognitive ageing might come down in part to a process of marginal gains.

7.3 Childhood IQ: a correlate and predictor of lifestyle

Childhood IQ, measured at age 11 for the Scottish Mental Survey of 1947, predicted all of the lifestyle factors measured almost 60 years later, as hypothesised. In general, higher intelligence in youth predicted the following dietary choices in older age: a higher caffeine consumption including a preference for coffee rather than tea; a higher alcohol consumption including a preference for wine over beer and spirits; a healthier diet including adherence to a Mediterranean-style diet compared to a more traditional diet. In addition to dietary choices, a higher childhood IQ was predictive of smoking avoidance and cessation of smoking, a lower BMI (but not underweight), increased physical activity, and a healthy lipid profile represented by a higher total- and HDL cholesterol and lower triglycerides, at age 70.

A few previous studies have examined the predictive value of cognitive ability for health behaviours such as smoking, diet, and alcohol consumption. People with higher early-life intelligence are more likely, decades later, to avoid smoking; eat more fresh fruit and vegetables, wholemeal bread, white meat, and fish; cook with vegetable oil; take more exercise; and comply in the long run with prescribed medications. People with lower intelligence in early-life are more likely, decades later, to eat chips, cakes and biscuits, and white bread; cook with animal fats; smoke; binge drink and have hangovers; and be obese or overweight (Batty, Deary, & Macintyre, 2006; Batty, Deary, Schoon, & Gale 2007a, 2007b; Chandola, Deary, Blane, & Batty 2006; Gale, Deary, Schoon, & Batty, 2007; Hemmingsson, Kriebel, Melin, Allebeck, & Lundberg, 2008; Taylor et al., 2003). The reports linking high childhood cognitive ability scores with a reduced risk of adult obesity also provide some indirect support for a relation of early-life mental ability with physical activity and diet (Chandola et al., 2006; Hart et al., 2003; Sørensen & Sonne-Holm, 1985).

Intelligence is a life-long stable trait that exerts powerful influences on educational successes, occupational status, use of health services, lifestyle, and recreational choices (Kilgour et al., 2010). Early-life intelligence is also an important risk factor for early death, predicting premature mortality better than many other commonly assessed risk factors including blood pressure and body mass index (Batty, Shipley et al., 2008). A meta-analysis of 16 independent studies concluded that a one standard deviation increase in intelligence scores assessed in youth was associated with a 24% lower risk of death over a follow-up period of 17-69 years (Calvin et al., 2011). Low intelligence is associated not just with premature death but a range of health conditions including obesity and the metabolic syndrome in early-mid-life, with type II diabetes and heart disease in later-life, and dementia in older age (Arden, Gottfredson, & Miller, 2009; Belsky et al., 2013; Der, Batty, & Deary, 2009; Wrulich et al., 2013).

One of the current challenges of cognitive epidemiology is to ascertain why lower childhood intelligence is associated with such a diverse range of adverse health outcomes (Schaefer et al., 2015). One possibility is that the skills captured in IQ tests, such as the ability to comprehend and reason, may be important in the successful management of an individual's health behaviours (Batty, Deary, Schoon, & Gale, 2007a). Essentially, cognition may influence the extent to which individuals manage their own risk for cognitive decline (Anstey et al., 2009). Higher levels of education and cognitive

ability are associated with better health and likely associated with higher levels of seeking help, diagnosis, and compliance with prescription medication.

7.4 Reverse causation

The key novel finding of this thesis is that, in addition to having predictive value for lifestyle choices over 60 years later, cognitive abilities at age 11 accounts for the majority of the cross-sectional association between cognitive abilities in older age and lifestyle factors, all of which have been reported to be involved in intelligence differences. Without early-life measures of cognitive ability it would have been plausible to conclude that adherence to healthy lifestyle practices significantly influences cognitive ageing, when instead, it is a lifelong association.

The relationship between risk factors and cognition may be more complex than medical outcomes. Often, there is the possibility of reverse causation, with prior cognitive ability causing the supposed 'cause' of cognitive ability in older age (Deary, Corley et al., 2009; Deary, 2010; Whalley et al., 2006). Throughout this thesis, the initial results pointed to a replication of the positive lifestyle-cognitive function associations, previously identified by others. However, in the same sample, the associations between mental ability at age 11 and the lifestyle factors studied at age 70, were just as strong as the contemporaneous correlations between cognitive ability and lifestyle at age 70. Moreover, adjusting for cognitive ability at age 11 reduced the latter correlations almost totally, and to non-significant levels, for many of the health behaviours. Therefore, exploring possible contributions to cognitive ageing yielded some remarkable insights into the role of reverse causation in cognitive epidemiology.

Some other instances of reverse causation have been reported in the cohorts derived from the Scottish Mental Surveys as a result of having extant childhood measures of intelligence. For example, McNeill et al. (2011) and Whalley et al. (2004) found evidence of reverse causation in the associations between supplement use and cognitive function; higher lifetime trait levels of IQ predicted supplement use rather than supplement use predicting IQ. In another study, associations between systemic inflammation levels and old-age cognition were indicative of reverse causality such that those with a lower IQ had an increased risk of higher inflammation in later-life rather than the converse (Luciano, Marioni, Gow, Starr, & Deary, 2009). In terms of health, what appears to be the effect of an illness state on cognitive ability in older age might in

part be the reverse: the effect of early-life cognition on the risk of developing the disease state. Hypertension, for instance, is associated with lower childhood IQ in middle age even after adjustment for other factors including social class and smoking (Deary, Whalley et al., 2009; Starr et al., 2004). Since childhood IQ is a strong predictor of cognitive function in later-life, the disease state may be acting as a marker of lower childhood IQ and this might explain, in part, any association with lower cognitive ability years later. Indirect support for this hypothesis comes from findings that lung function (forced expiratory volume in one second) and blood pressure in later-life are associated with childhood intelligence (Deary, Whalley, Batty & Starr, 2006; Richards, Strachan, Hardy, Kuh, & Wadsworth, 2005; Starr et al., 2004). Both of these factors are variables which have been explored as putative contributors to cognitive ageing, so it is important to be cognizant of reverse causation, with prior intelligence being associated with variation in them in later-life.

The possibility of reverse causation should be tested in studies of older adults. Those able to control for prior intelligence—and thus control for reverse causation—are rare, but necessary. It may be that the results in this thesis point to a dynamic cycle of cognition and lifestyle, reflecting associations among variables, rather than indicating the direction of effects. They could be interpreted as suggesting that: (1) intelligence is a lifelong trait, and with the exception of smoking, physical activity and alcohol consumption, lifestyle factors have little effect on cognitive test performance in older age; (2) higher intelligence leads to better health behaviours, and that better health behaviours result in better cognition/less cognitive decline; (3) a third variable produces both better health behaviours and better cognition; this is discussed in the next section.

7.5 Overall system integrity: an alternative explanation

The work in this thesis demonstrates that intelligence test scores from childhood are associated with lifestyle factors in older age. Therefore, the cross-sectional ‘variable X versus cognitive ability scores’ finding in older age might—in part or whole—be the result of reverse causation: intelligence traits from early-life affect later-lifestyle and health. Another possibility is that the cross-sectional correlation is caused by some third—confounding—variable or set of variables and that the correlation is spurious, being the result of some more basic factor(s) that affect both the apparent cause and effect. Some researchers have proposed that IQ may act as an index of overall system

integrity. The system integrity hypothesis derives from work on human cognitive epidemiology and, put simply, proposes that intelligence could be an indicator of a body that has generally been put together well, and which can respond well to stressful challenges from the environment (allostatic load) (Deary, 2010; 2012b). Therefore, higher intelligence may be a marker for a general latent trait of an originally well-functioning body. Kilgour et al. (2010, p99) states that there is evidence to suggest that "...IQ and its neurobiological infrastructure is in some unknown way linked to the overall efficiency of the brain in its capacity to maintain the integrity of central regulatory physiological systems." Deary (2012b) makes it clear that the system integrity hypothesis is not the same as the common cause hypothesis of cognitive ageing. In the system integrity hypothesis it is thought that there are correlations among complex bodily systems in terms of their efficiency in the healthy state. The common cause hypothesis arises from findings such as the discovery that age-related changes in cognitive abilities are correlated with age-related changes in sensory functions such as vision, hearing, and balance (Anstey & Smith 1999; Anstey, Hofer, & Luszcz, 2003; Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994; Salthouse, 1998). These early findings were referred to as the 'common cause hypothesis' in which age-related cognitive and physical changes were thought to be the outcome of a loss in the integrity of brain and general bodily physiology over time. So, the common cause and system integrity hypotheses are now thought to be distinct in that, essentially, the former is concerned with coupled age-related loss across bodily systems, i.e. the preservation of function over time, whereas the latter is based on the initial establishing of and correlations between optimal bodily systems, i.e. prior to ageing effects (Deary, 2012b). The well-documented association between higher childhood IQ and prolonged survival also may be viewed as support for this theory of system integrity (Calvin et al., 2011).

Recent evidence suggests that associations between intelligence, disease, and mortality arise because less intelligent people actually 'age' faster than their more intelligent peers (Schaefer et al., 2015). The concept of accelerated aging arises from observations that age-related chronic diseases are preceded by a gradual accumulation of damage to multiple organ systems that begins in the first half of the life course (Ben-Shlomo & Kuh, 2002). There is evidence that (very) early-life intelligence predicts biological age measured more than three decades later. Those with a lower pre-school IQ looked older, scored as biologically older on a 10-biomarker algorithm measuring metabolic,

hepatic, renal, cardiovascular, pulmonary and immune functioning, and had 'older' cardiovascular systems. Importantly, these results suggested that the associations between intelligence and midlife biological age did not arise from early-life health problems or early socioeconomic disadvantage, and can even be seen when intelligence is assessed before formal education has begun (Schaefer et al., 2015). The authors concluded that 'accelerated ageing' may be one of the factors linking low early-life intelligence with increased rates of morbidity and mortality. While other studies have established a link between low intelligence and increased morbidity and mortality (Calvin et al., 2011; Der et al., 2009, Whalley & Deary, 2001), the above findings suggest that lower early-life intelligence may actually accelerate the ageing process in general and lead to a range of negative age-related health outcomes including cognitive health.

There is no denying that the complex web of associations in ageing trajectories is plausibly connected via the system integrity hypothesis and that any deterioration in cognitive function may be the result of overall bodily deterioration, the causes of which are shared. Whether or not this is the case remains to be determined. Intelligence **may** be a marker of brain health which reflects overall system integrity (Deary, 2012b). However, quite apart from the observed associations between intelligence and better health behaviours, individuals with a higher IQ may also have better access to health care, safer occupational and residential environments leading to lower stress, and adequate sleep (Deary, Weiss, Batty, 2010) which may independently impact upon cognitive health.

7.6 The role of socioeconomic status

As expected, in each of the seven studies, a more professional adult occupational social class (SES) was associated with healthy behaviours and was a confounder in the associations between lifestyle and cognitive function. Untangling the effects of SES and intelligence is problematic, as stated previously in the thesis. There is some suggestion in the literature that physical health is more closely associated with intellectual ability than SES, at least in adolescence (Lubinski & Humphreys, 1992). That said, other research also shows that children's early SES influences their intelligence (Von Stumm & Plomin, 2015) and that socioeconomically advantaged children may be more likely to benefit from resources that promote healthy ageing.

Some researchers (Hagger-Johnson et al., 2012; Singh-Manoux, 2005) have suggested that SES, rather than confounding the associations between lifetime cognition and lifestyle, in fact acts as a mediator, given that adjusting for SES did not substantially attenuate the association between IQ and lifestyle. SES could mediate the association in that people with higher intelligence are more likely to work in more professional jobs, have more income, and these jobs in turn may provide safer environments, so that people with higher intelligence tend to be healthier and therefore live longer (Whalley & Deary, 2001). For example, in the caffeine analyses (as in the other analyses), it is possible that IQ is exerting its effect through social class. That is, persons who end up with better cognitive function at age 70 tend to be higher in IQ allowing them to achieve a higher SES and to have adopted more high class behaviours such as 'fancy' coffee intake. In order to test this we ran a mediational analysis to see how much of the IQ-coffee relationship was mediated by SES. The amount of the relationship between age 11 IQ and ground coffee consumption accounted for by social class as a mediator represented 59.1% of the direct effect. Based on this finding, the conclusion was that adult social class acts as a significant mediator (accounting for over half of the relationship between age 11 IQ and ground coffee) consumption in this cohort of Scottish 70 year olds. This supports the idea that having a higher age 11 IQ enables people to achieve a higher SES (via education, employment, income) and that it is this indirect pathway which may lead to a more 'cosmopolitan' lifestyle. This reinforces the already widely documented finding that social class has an important role to play in the investigation of IQ and lifestyle.

Intelligence is correlated significantly with childhood and adult SES (Breen & Goldthorpe, 2001; Deary et al., 2005; Marioni et al., 2014). Singh-Manoux (2005) proposed that childhood socio-economic position might be a confounder of any IQ-lifestyle association, and adult SES might be a mediator. To date, it seems that childhood SES does not substantially attenuate the association, and that intelligence and adult SES may have some shared and independent influences on health outcomes (Deary & Batty, 2007). Recent findings suggest some shared genetic contributions to intelligence and SES; some of the variance in SES can be found in DNA variation, some of which is shared with the DNA variation that causes some individual differences in intelligence (Marioni et al., 2014). Therefore, even apparently different types of markers of individual differences may reflect shared aetiology, and tap something at least partially overlapping, potentially leading to spurious associations.

Chapter 8 - Implications of Findings

8.1 Implications for cognitive ageing research

These studies demonstrate how difficult it is to establish causal relationships involving cognitive function and lifestyle. Although these studies are observational, they illustrate the potential complexities of the interaction of cognitive function with behavioural factors.

These results are novel and the findings advance current knowledge on successful ageing. Collectively, the results of these studies indicate that the relationships between healthy lifestyles and better cognition may be wholly or partly attributable to confounding by a higher lifetime IQ, and by association SES, and that many previous studies may have prematurely ascribed a causal influence of lifestyle factors without knowing trait (prior) IQ level from earlier in life. Instead, the association may be indirect or bidirectional, or a more complex dynamic association as discussed above. Prior conclusions may be erroneous given the absence of strong tests that include potential 'third' variables. From a scientific perspective, this means that proper statistical consideration should be given to lifetime IQ levels, wherever possible. The findings from this thesis place childhood IQ firmly within the framework of the lifestyle-cognition relationship and are useful in reconsidering results of previous epidemiological investigations, which have typically focussed on a direction of causation suggestive of direct benefit derived from certain lifestyle behaviours in later-life.

This data from the LBC1936 suggests that moderate alcohol (particularly wine) consumption, smoking avoidance (and smoking cessation), and increased physical activity, might contribute to successful ageing in terms of performance on several major ageing-related cognitive domains. Individuals who participated in these healthy behaviours showed greater maintenance of IQ in older age. These studies provide initial support for the premise that these three health behaviours might provide protective effects on cognition in aging. As stated in the respective papers, the effects when found were small, and further replication is required. Ongoing research is needed to verify these findings and to identify and isolate specific factors that positively influence cognitive changes that occur with aging.

In terms of alcohol consumption, to date, there is no consensus in the literature that moderate wine consumption has a protective effect on cognitive function, or of the definition of moderate intake, not to mention a 'beneficial' level (Panza et al., 2009). The evidence to support the role of physical activity in successful ageing may be compelling but there are similar problems and controversies within the available evidence and questions remain to be answered. Given that physical activity is an umbrella term for an enormous range of actions, a critical issue is whether there are minimal and optimal levels of activity that benefit healthy cognitive ageing. Similarly, it is unclear where physical activity ends and physical exercise begins. Often studies do not clearly distinguish between activity and exercise and therefore cannot examine their differential impact on cognitive outcomes. Furthermore, it is uncertain at this point whether the benefits of physical activity are a result of exercise or the reduction in sitting which has the most significant role in health cognitive ageing, given the recent research interest in the detrimental health effects of sedentary behaviour. The LBC1936 cohort is ideally placed to investigate this research question in the future as cohort members are, at present, taking part in an activity monitoring study which measures sedentary patterns (sitting and standing behaviour) using an activity monitor (activPAL physical activity monitor, PAL Technologies Ltd, Glasgow, Scotland, [Grant, Ryan, Tigbe, & Granat, 2006; Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011]) worn on the leg and completing self-report questionnaires.

In the future, intervention studies should provide more robust evidence for the effects of lifestyle factors such as diet and nutrition, but to date few have been done, and most are of short duration in older adults, which may explain the largely negative results.

8.2 Implications for public health professionals

If lifestyle variables have a positive impact upon cognitive ageing, such findings are important, perhaps more so than genetic or biological influences, because they are amenable to intervention. Clinicians working with older adults in a variety of settings can incorporate knowledge of the beneficial effects of physical activity and smoking avoidance into health promotion for older adults. Assessment of older individuals should include a review of health behaviours and participation in activities.

Encouraging either initiation or continuation of participation in physical pursuits and providing information and support for smoking cessation should become standard treatment recommendations. Habits such as smoking, however, are hard to break, and

in the UK, the uptake of healthy behaviours remains poor. For example, recently published results from the National Diet and Nutrition Survey suggest that fewer than a third of adults are meeting the recommended portions of five fruit and vegetables a day (Public Health England, 2014). Most older adults do not get an adequate amount of exercise. According to new UK guidelines, older adults should do at least 150 minutes per week of moderate-intensity activity or 75 minutes of vigorous activity or a combination of both, on most days of the week, lasting ten minutes or more (Davies, Burns, Jewell, & McBride, 2011). Few achieve these guidelines (Jefferis et al., 2014). Barriers to regular exercise in older age have been identified and include health concerns, pain, fear of injury, lack of confidence, as well as misconceptions about exercise (O'Connor & Kraft, 2013). Our results suggest that exercise may be a promising vehicle for maintaining cognitive functioning in older adults and knowledge that physical activity prescribed for common chronic conditions such as cardiovascular disease and diabetes may have protective cognitive effects may increase adherence to an active lifestyle in older adults. However, an important area in need of further research is determining ways in which these barriers could be overcome.

In addition, older adults reporting cognitive declines (such as memory loss) should be encouraged to undergo cognitive testing. Testing that distinguishes normal versus pathological changes will enable clinicians to provide reassurance to most older adults that they are experiencing changes as a normal part of the aging process. Reassurance may alleviate undue anxiety, depression, and social isolation due to fear others will notice cognitive decline.

The possibility that lifetime stable levels of 'trait' IQ accounts for the majority of some of the lifestyle-cognition relationships in older age has important implications for the study of cognitive ageing and for those interested in translating such observational findings into interventions aimed at reducing or delaying age-associated decline. Another direction for future studies is examining ways to identify as early as possible those most susceptible to poor cognitive health in late life who would stand to benefit most from the strategies identified in the current thesis as potentially beneficial.

Chapter 9 - Methodological Considerations

9.1 Strengths

The relative strengths and limitations of these studies are documented in each article but an attempt will be made to consider them here. Clearly, the major strength of these studies was the availability of IQ data at two distant time points (age 11 and age 70) in a large sample of individuals. This permitted an examination of the contribution of various lifestyle factors to relative cognitive change on this measure from childhood to late adulthood. There was a further advantage of examining childhood cognitive ability before any detriments caused by chronic illness, and before the uptake of health behaviours; such modifiable behaviours are usually established during young adulthood (Steptoe et al., 2002). The data were derived from a cohort who shares the same year of birth. The narrow age cohort is an important design advantage given that health behaviours, such as smoking patterns, can change over time; there is no conflation of chronological age with a birth cohort sample due to generational effects. This is important to bear in mind as age related differences between individuals do not necessarily imply ageing; different generations or cohorts are subject to particular environmental exposures and opportunities (Hofer, Flaherty & Hoffman, 2006).

Other significant strengths of these studies include comprehensive cognitive data, derived from a validated psychometric approach, with multiple tests of important cognitive domains at age 70 and detailed data on health behaviours, such as quantity and duration of smoking in addition to current smoking status, and amount and types of caffeine and alcohol consumption.

Establishing lifestyle contributions to individual differences in older-age cognition using associational studies is challenging due to the potential mediating and/or moderating effects of other lifestyle and environmental factors. The LBC1936 sample has data on a wide variety of sociodemographic and health factors. This made it possible to adjust for a comprehensive range of potential confounders.

9.2 Limitations

The findings of these studies should be considered within the context of their limitations. Although limitations of each of the reported studies are discussed in their respective papers, a brief discussion of some general limitations follows. Although the

use of a narrow age group is advantageous, this may limit the generalisability of results. Second, the use of self-reported health behaviours is open to recall bias, especially among older participants. For example, under-reporting of smoking history or mis-reporting of dietary information may be a potential confounder of the data. The use of self-report medical history and relatively minimal exclusion criteria may also result in a sample including participants with health conditions that are not severe enough to prevent their participation in the study, but are known risk factors for neuropathology and likely to affect cognitive performance (Nebes et al. 2006). Third, given that our sample is self-selecting, it is biased towards high-functioning, well-educated, motivated volunteers – as is the case in many studies of cognitive ageing (Nebes et al. 2006). The mean childhood tests scores for Edinburgh in the SMS1947 were the highest in the country and so this likely reflects a stable lifelong regional difference to some degree (the mean for the 1947 population was 36.70 compared with the Edinburgh educational area of 40.28; Scottish Council for Research in Education, 1958). The higher ability of the LBC1936 cohort compared with the SMS1947 population may be partly explained by a survivor effect, whereby higher-ability individuals were more likely to reach their 70s in relatively good health and thus be eligible for recruitment into the follow-up studies, and able to attend for assessment. Having said that, it must be noted that the age 11 IQ scores of our sample spans a wide range, and therefore, represent a broad range of abilities. Moreover, as mentioned in several of the papers included in this thesis, any restriction in range of abilities would, if anything, lead to an underestimation of associations and effect sizes.

9.2.1 Type I errors

One limitation of studies of the type conducted in this thesis is that a large number of statistical tests are often carried out because of the variety of predictors and cognitive tests studied. Of course, having a rich list of predictors and an extensive cognitive battery are strengths of the LBC1936. However, given that this thesis adopted an analytic strategy that relied upon multiple testing of data, the possibility of type 1 errors (e.g. the probability of rejecting the null hypothesis when the null hypothesis is true) must be acknowledged. The associations that remained significant in the final models were at either the 5% or 1% level, so would often have been abolished by a conservative correction for multiple testing. However, with the relatively small sample sizes and expected modest effect sizes, adopting stricter alpha levels would have increased the probability of type 2 errors. Although the tests used are recognised to be

sensitive, clearly the results need replicating in other populations before they are accepted as robust. The validity of any associations is more accurately tested by future replication studies (Lykken, 1968) than by relying on strict alpha levels that may preclude discovering potentially interesting findings in the first place.

9.3 Cross-sectional vs longitudinal approaches to studying cognitive ageing

There are clear difficulties in establishing causal relationships involving cognitive function and lifestyle. Although the studies in this thesis are cross-sectional, they illustrate the potential complexities of the associations between cognitive function with behavioural factors. Cross-sectional designs are useful for preliminary investigations and hypothesis generation and are faster and less expensive to conduct. However, the inferences that can be drawn regarding age differences in cognitive performance are limited. Measurement at a single point is a function of individual differences, cumulative development change as well as within-person variability and measurement error (Hofer & Piccinin, 2010). Studies on older populations followed over short periods have generally shown an association between lifestyle and cognitive impairment (Buchman et al., 2012; Iwasa et al., 2012). But the likelihood of reverse causation makes the interpretation of short-term studies difficult. In order to overcome the biases inherent in cross-sectional measurement, to better understand what normal cognitive changes can be expected with aging, and to discover the mechanisms that explain adult development, researchers are now recognizing the importance of longitudinal studies of ageing (Hofer & Piccinin, 2010; Salthouse, 2010b; Schaie & Hofer, 2001). Therefore, research designs in the future must move beyond convenient cross-sectional studies to longitudinal trials that can establish causal relationships and control for the numerous confounding factors such as lifestyle variables that may impact cognition. Sensitive outcome measures must be identified and used consistently among investigators to enable synthesis of findings from multiple studies.

Further simultaneous examinations of lifestyle effects on both cognitive ability levels and change are required. To date, evidence of concurrent associations of a factor with cognitive ability do not necessarily generalise to significant associations with cognitive change. Although prior ability predicts the level of later ability, there is evidence that it is not related to the degree of change across time. As was noted in the introduction to the thesis, the distinction between level and change is an important one. The stability of

cognitive ability over long periods of time is well-established (from the LBC and other longitudinal studies), however, reports of the association between early ability and cognitive change measured some decades later have been inconsistent (e.g. Gow et al., 2008; Bourne, Fox, Deary, & Whalley, 2007). The work in this thesis is relevant to the debate, which has recently emerged, on preserved differentiation vs differential preservation proposed by Bielak and colleagues (Bielak, 2010; Bielak, Cherbuin, Bunce, & Anstey, 2014; Gow, Mortensen, & Avlund, 2012; Salthouse, 2006). At the core of this theory is the critical question of whether lifestyle factors alter the trajectory of age-related cognitive decline (differential preservation) or are associated with enhanced baseline cognitive ability (preserved differentiation). In searching for determinants of cognitive ageing, researchers aim to identify evidence of differential preservation. The work by Bielak on physical activity and cognitive performance over time (in those aged 20-72) supports preserved differentiation, where physically active adults have higher initial cognitive ability, and that this advantage is maintained over time (Bielak et al., 2014). In contrast, Gow, Mortensen et al., (2012) found that physical activity level at both ages 60 and 70 predicted change in general cognitive ability from ages 60 to 80, supporting differential preservation. Bielak et al. (2014) concluded that differential preservation may be evident in the older age bracket, once the effects of health and other risk factors are more apparent.

To date, relatively little is known about the longitudinal effects of these health behaviours on cognitive decline (Cadar et al., 2012) and this should be a research priority given that patterns of behaviours tend to develop over decades. In the UK Whitehall Study, obesity, alcohol and smoking have been shown to affect cognitive function over 10 years (Hagger-Johnson et al., 2013; Singh-Manoux et al., 2012). The Scottish Mental Surveys of 1932 and 1947 have yielded valuable insights into cognitive ageing thus far, and studies of this type become more feasible as individuals grow older in continuing longitudinal studies.

Fortunately, a large number of longitudinal studies have now been established to investigate the relationship of a range of factors to cognitive decline in older adults, including, for example, the Rush Memory and Ageing Project, the Nun Study, the Victoria Longitudinal Study, the Health and Retirement Study (HRS), the English Longitudinal Study of Ageing (ELSA), the Whitehall II Study, the 1946 National Birth Cohort Study, the Maastricht Ageing Study, as well as the Lothian Birth Cohort 1921 and 1936 studies. In addition to risk factors for cognitive decline and dementia,

longitudinal studies can identify protective factors associated with the maintenance of cognitive function among participants considered to exhibit 'successful ageing'. Despite the advantages provided by longitudinal studies of cognitive aging compared to cross-sectional studies, it is important to consider issues such as attrition, survival effects, missing data, and practice effects when interpreting the results of longitudinal studies (Schaie & Hofer, 2001).

9.4 Pre-clinical cognitive impairment

There are many challenges to health behaviour assessment in older people because of disabilities such as loss of hearing, mobility and eyesight. Although clinically significant cognitive decline (and the onset of dementia) occurs in older age (over 65 years) it is important to take into consideration that cognitive impairment develops slowly and silently over the preceding decades (Petersen et al., 2006; Small, Stern, Tang & Mayeux, 1999). Neuroimaging studies show pathological changes in midlife before any clinical signs appear (Fox et al., 2001). Inevitably, in older age samples, some participants are likely to have some degree of pre-clinical cognitive impairment. The possibility that cognitive decline influences health behaviours should be borne in mind in the interpretation of observational studies of the influence of lifestyle factors such as dietary intake on cognition in later-life. Using dietary intake as an example, there is some evidence that dietary data from older people may be less reliable than those obtained from younger people (Pope, Kritchevsky, Morris, & Block, 2007). The major concern is the possibility that age-related decline may bias results and distort associations between diet and cognitive function.

Additionally, care should be taken when studying the effect of diet on cognitive impairment in late life since there is the potential for preclinical disease processes to affect dietary intake in terms of food choices. Observational studies cannot prove whether nutritional status is a cause or consequence of an impaired cognitive status (Del Parigi, Panza, Capurso, & Solfrizzi, 2006). Cognitive impairment may impact on nutrition via the ability to shop for groceries, cook healthy meals, read and understand recipes, and remembering to eat regular meals. In the LBC1936, asking participants about a medical history of dementia-related problems and the use of the MMSE as a screening tool for cognitive pathology, minimises the likelihood of those with cognitive deficits being included in the analyses, but this exclusion process is not infallible.

9.5 Memory: the lack of associations with lifestyle

In these data, there was little evidence of lifestyle associations with memory function, with the exception of a small, positive association with moderate alcohol intake. The lack of associations is slightly puzzling given that episodic memory and working memory decline with advancing age. Nevertheless, large-scale population-based studies document well-preserved memory functioning in many older individuals (see Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). Another explanation might relate to the measurement of memory function. The memory factor used in the thesis was a composite of several memory tasks comprising immediate- and delayed episodic, and working memory. Letter-Number Sequencing is primarily a working memory test involving manipulation of numbers and letters by the participant. Digit Span Backwards is commonly used as a working memory test but has clear episodic memory overlap. Furthermore, Spatial-Span Forwards and Backwards tap other cognitive processes such as spatial awareness. Perhaps using a memory factor derived from a subset of purely episodic memory tests or a subset of primarily working memory tests might have given different results. From a biological standpoint, there are studies of cardiovascular risk factors and memory that also report a lack of association (Knopman et al., 2001; Singh-Manoux & Marmot, 2005).

Chapter 10 - Future Directions and Concluding Remarks

10.1 A life-course approach

It is increasingly clear that cognitive impairment has a long preclinical phase and this presents another good reason for longitudinal investigations. Like other chronic diseases such as CVD, the impact of environmental factors on cognitive health likely occurs long before symptoms appear. Examining these associations using a life-course approach (Ben-Shlomo & Kuh, 2002; Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003; Whalley et al., 2006) provides an important opportunity to identify the nature and timing of different environmental influences on cognition. This approach acknowledges that risk and protective factors can exert their critical influences at different ages (Fratiglioni, Paillard-Borg, & Winblad, 2004). For example, there is evidence to suggest that early-life is a critical period for the development of cognitive reserve (learning and education) (Stern, 2009) whereas lifestyle behaviours including those that influence cardiovascular and metabolic risk become more influential in midlife, although some such as diet and physical activity can be traced back to youth (Kuh & Cooper, 1992; Mikkilä, Räsänen, Raitakari, Pietinen, & Viikari, 2004). A particularly salient example of time-dependent effects of lifestyle factors on cognition is serum cholesterol, whereby the risk associated with high (total) cholesterol levels changes with age; high total serum cholesterol levels in middle age, but not in older age, associate with cognitive impairment in later-life (see Corley et al., 2015; van Vliet et al. 2009). A systematic review by Lee, Back, Kim, Kim et al. (2010) found evidence that midlife health behaviours contribute to cognitive health in later years, suggesting cumulative effects of healthy lifestyles.

In fact, influences clearly extend back as far as the prenatal environment, and other early influences, may include breastfeeding and early-life nutrition (Benton, 2008; Kramer et al., 2008). Therefore, there is a long-term aetiology of cognitive change. It is imperative that future studies investigating environmental risk factors for cognitive decline and dementia are conducted from a life-course perspective in order to disentangle the temporal order of the relations between these factors and cognitive function.

10.2 A lifestyle pattern approach

It has been established that longitudinal analyses using a life-course approach are required in order to investigate the influence of lifestyle factors on cognitive change over old age. A second promising avenue for future research is to examine lifestyle patterns. Lifestyle factors are often considered in isolation, which, although convenient, may not accurately reflect the way in which individuals actually experience these factors. Very little work has focused on the combined influence of these behaviours on cognitive functioning with a few exceptions (Cadar et al., 2012, Sabia et al., 2009; Lee, Kim, & Back, 2009; Myint et al., 2011). Approaching them from a multivariate perspective would allow a more realistic examination of the ways in which individuals participate in a range of somewhat related behaviours and permit the identifications of which factors have a more prominent association with cognition above other influences in older age.

A study of London civil servants (Sabia et al., 2009) highlighted that the number and duration of healthy behaviours in mid-life were associated with subsequent cognitive function in later-life. Later work from the same British occupational cohort found that the cognitive benefits of healthy behaviours appeared to increase linearly as a function of the number of healthy behaviours present. Additional benefits were observed for other domains including respiratory and cardiovascular functions (Sabia et al., 2012). Similarly, data from the Suwon Longitudinal Aging Study showed that a combination of multiple positive life behaviours (such as smoking, social activity and vegetable consumption) were associated with better cognitive ability (Lee et al., 2009). A further study showed an increment in global cognitive function scores with each additional healthy lifestyle factor (Lee et al., 2009). Since these behaviours tend to cluster, the extent to which the apparent effects of one health behaviour are attributable to (i.e. confounded by) another is unclear.

The determinants of healthy ageing might be taken as implying that their effects operate independently, but this is clearly not the case; they also determine one another. For instance, physical activity and exercise are increased by active social networks (Leroux, Moore, Richard, & Gauvin, 2012) and family support (Yuan et al., 2011) while physical activity has been demonstrated to influence appetite and the consumption of a healthy diet. Similarly, diet and eating behaviour have been shown to be associated with the quantity of social contact (Sahyoun & Zhang, 2005) and the eating

environment (Carrier, West, & Ouellet, 2009). Evidence suggests that smokers have poorer dietary choices than non-smokers (Woodward, Bolton-Smith, & Tunstall-Pedoe, 1994). With these findings in mind, there is more work to be done to clarify how each determinant exerts its effect on healthy cognitive ageing i.e. directly or indirectly through the other determinants.

In addition to influence of one health behaviour on another, further work on the effect of interactions between lifestyle behaviours on cognitive health is recommended. For instance, the Mediterranean diet may only be an effective protective factor for AD in those who exercise (Scarmeas, Luchsinger et al., 2009). Mediating factors and gene-environment interactions may operate and influence outcomes in different population groups (Coppede, Mancuso, Siciliano, Migliore, & Murri, 2006). For example, one study found that adherence to the Mediterranean diet was associated with cognitive decline in non-diabetic but not diabetic individuals, implying that diabetes mellitus may be one of the mediating factors (Tsivgoulis et al., 2013).

Just as foods are not consumed in isolation but as part of a complex dietary pattern, health behaviours are part of a greater lifestyle pattern or way of life. There is evidence that behaviours related to a Mediterranean way of living, which has been shown by some studies to be associated with cognition, is also associated with social interaction, participation in leisure activities, and sleep quality. Yannakoulia et al (2015) suggest that lifestyle patterns, comprising a constellation of health behaviours, may constitute a new research and public health perspective. For instance, lifestyle patterns could be derived using a posteriori approaches (similar to the methods used to ascertain dietary patterns) via data reduction to identify underlying dimensions of a range of health behaviours potentially associated with cognitive ageing or other health outcomes. To date, studies identifying health behaviour clusters have been limited. A German study identified five homogenous clusters in an older population: an 'ideal' health-related behaviour pattern; two clusters were smokers and problem drinkers who had other unhealthy behaviours; and two clusters had a mix of healthy and unhealthy behaviours (Schneider, Huy, Schuessler, Diehl, & Schwarz, 2009). Perhaps unsurprisingly, clustering of health behaviours is more pronounced at both ends of the spectrum (Conry et al., 2011), with more people than expected having all or none of the lifestyle risk factors. The clustering of unhealthy behaviours has also been found to have synergistic effects, which means that a combination of health behaviours is more detrimental to health than would be expected from the added individual effects of

health behaviours and this impacts upon longevity (Kaczynski, Manske, Mannell, & Grewal, 2008; de Groot, Verheijden, De Henauw, Schroll, & Van Staveren, 2004). Those with four risky health behaviours (poor diet, smoking, physical inactivity and excessive drinking) have been found to die on average fourteen years earlier than their counterparts without these health behaviours (Khaw et al., 2008). Further work on the synergistic effect of these lifestyle behaviours on age-associated cognitive decline is a promising direction for future studies.

10.3 The use of MRI techniques

Another key issue when examining the association between lifestyle variables and cognitive health with ageing is the underlying mechanism of action. The relatively recent ability to measure brain biomarkers thought to be associated with pathological processes has provided a way to examine effects of lifestyle on brain pathologic burden and cognitive abilities in cognitively normal older adults (see Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014). With the increased availability of brain imaging technology, it is likely that studies will be working toward a comprehensive integrated model approach of cognitive ageing, combining multiple predictor pathways including lifestyle factors and a range of biomarkers reflecting beta-amyloid plaque burden, cerebrovascular burden, neural injury and cognitive outcomes (See Wirth et al., 2014; Vermuri et al., 2012).

The emerging consensus is that intelligence relies upon undisrupted information transfer among brain regions along white matter fibres (Deary, Penke et al., 2010). White matter is especially prone to age-related cognitive decline, and white matter lesions have been extensively studied in elderly subjects. One study with cognitive data spanning several decades found a significant association between childhood IQ and white matter integrity in old-age (Deary, Bastin et al., 2006). These findings suggest that in addition to the direct contribution of white matter integrity to intelligence, higher intelligence might result in behaviours across the life-course that promote white matter integrity. Physical activity is a good example of the effect of lifestyle on brain integrity. There is evidence that physical activity affects brain structure. In humans, aerobic exercise training can increase hippocampal volume by as much as 2%, which equates to reversing age-related volumetric declines by 1-2 years as well as improved memory functioning in older people (Erickson et al., 2011). Hippocampal volume has also been found to be a predictor of verbal memory functioning (Ystad et al., 2009),

spatial memory (Erickson et al., 2011) and general memory abilities (Chen, Chuah, Sim, & Chee, 2010).

10.4 Combining genetics and environmental methods of research

It is possible that intelligence and brain (white matter) integrity have, from an early age, overlapping sets of genetic and environmental influences (Chiang et al., 2009; Deary, Penke et al., 2010). In epidemiology, it is common to define many factors as environmental, despite strong genetic input. For example, data from the Generation Scotland: Scottish Family Health Study, found that education, income, smoking, and fruit and vegetable consumption all had substantial heritability, genetic correlations with general intelligence, and bivariate heritability (Luciano et al., 2010). McGue et al. (2014) found a moderate to strong genetic contribution (that is stable over age) to individual differences in six lifestyle factors in a Danish twin study, ranging from 32% for the diet measure and 69% for the smoking measure. Twin studies are ideal for examining the interplay between genetic and environmental influences on ageing phenotypes. In fact, the authors state that twin studies,

“dispel the dichotomy that is sometimes made between lifestyle and genetic contributions to ageing. In particular, a finding that lifestyle factors are heritable would suggest that, rather than being exogenous, lifestyles reflect at least in part qualities that are intrinsic to the individual.” (McGue et al., 2014 p776).

Therefore, individuals likely construct lifestyles in part to complement and reinforce underlying genetically influenced dispositions and talents including IQ. The heritable nature of lifestyle factors implies that the behavioural and genetic contributors to ageing processes are not necessarily conceptually distinct but rather reflect the complexity of gene-environment interactions in ageing. Given the powerful synergy between these two sets of conditions, the ultimate strategy would be to discover interventions to prevent cognitive decline, and dementia syndromes, by combining genetic and environmental methods of research.

10.5 Future planned work

These results are preliminary; many questions remain. The LBC1936 study is ongoing, currently on the fourth wave of assessment, and ideally placed to investigate these associations longitudinally. In addition to further planned analyses of smoking and body mass index, during wave 4 (due for completion in 2016), participants have completed a second FFQ permitting investigations of diet and cognitive change over 10

years. Future longitudinal studies on the relationship between lifestyle and cognitive change over a decade in the LBC1936 would allow causal inferences to be made in relation to the study objectives.

Evidence is emerging that an increased risk of cognitive decline and dementia is mediated by increased activation of inflammatory processes (Kuo et al., 2005; Dziedzic, 2006; see also Whalley et al., 2006). Levels of peripheral inflammatory markers such as C-reactive protein and Interleukin-6 are associated with cognitive decline, supporting an etiologic role for inflammation in cognitive aging (Gimeno, Marmot, & Singh-Manoux, 2008, Singh-Manoux et al., 2014). A recent study found that high levels of Interleukin-6 halved the odds of ageing successfully 10 years later and was associated with increased odds of cardiovascular disease (Hagger-Johnson et al., 2013). However, high levels of inflammatory biomarkers are associated with behavioural factors. High concentrations of CRP, for example, have been reliably linked with obesity (Herder et al., 2007; Timpson et al., 2005; and see Calder et al., 2011), the metabolic syndrome (Eckel, Grundy & Zimmet, 2005) and smoking (Bazzano, He, Muntner, Vupputuri, & Whelton, 2003). Using inflammatory biomarker data in the LBC1936, I plan to investigate the relationships between chronic low-grade inflammation and cognitive decline, and whether any associations exist independently of health behaviours. This would extend some initial analyses (Corley, Kyle, Starr, McNeill, & Deary, 2015) which suggest that nutrient dense dietary patterns in the LBC1936 are associated with lower levels of inflammatory biomarkers in older age.

10.6 Concluding remarks

The search for malleable determinants of cognitive ageing is a research priority. The identification of such risk and protective factors has the potential to inform public health interventions aimed at reducing disability, improving quality of life and decreasing social, healthcare and economic challenges associated with an ageing population. The individual variation in cognitive ageing trajectories is an indicator that certain environmental factors may exert a degree of influence but the identification of these likely small effects is problematic. The results from this thesis suggest that cognitive function in later-life may, to a small extent, be influenced by some lifestyle choices such as moderate alcohol intake, smoking avoidance, and physical activity. However, the key novel finding from this series of studies is that, in addition to having predictive value for lifestyle choices over 60 years later, cognitive ability at age 11

accounts for the majority of the cross-sectional associations between lifestyle factors and cognitive abilities in later-life. Many of the associations between positive health behaviours (e.g. moderate caffeine and alcohol consumption, and healthy dietary patterns) and cognitive abilities in old-age were confounded by a higher lifetime stable IQ and SES and the possible influence on these factors on the adoption of health behaviours in adulthood.

Insufficient attention is paid to the possibility of reverse causation. The effects of lifestyle on cognitive abilities in older age are difficult to disentangle from the effects of cognitive ability on lifestyle and from other confounding variables. Intelligence is important in everyday decision making; this would probably influence decisions made with regard to health management (Deary, Penke et al., 2010). Thus, people with higher early-life ability are more likely to adopt a lifestyle pattern which protects against cognitive decline. That differences in childhood IQ are related to differences in lifestyle choices in later-life, suggests that these relationships begin early and persist over the life-course. These findings point to the importance of taking a life-course perspective to the study of lifestyle and cognition and in designing interventions to delay cognitive decline (Gatz, Prescott & Pedersen, 2006). They also point to the importance of research in the early years of life which can contribute information toward maximising cognitive ability in childhood and youth, given their associations with life-long health.

The conclusions from this thesis are two-fold. (1) There may be a dynamic cycle involving cognition, self-management of health and ultimate cognitive outcomes. (2) Individuals can, to some extent, play an active role in their cognitive health across their life course, although further longitudinal studies with long follow-up periods are crucial.

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Appendices

APPENDIX A Publications submitted for PhD by research publications

Corley et al. (2010) *Psychosomatic Medicine*
Corley et al. (2010) *Psychology and Aging*
Corley et al. (2011) *Neuropsychology*
Corley et al. (2012) *Journal of Psychosomatic Research*
Corley et al. (2013) *International Psychogeriatrics*
Corley et al. (2015) *International Psychogeriatrics*
Gow et al. (2012) *Psychology and Aging*

APPENDIX B Other publications 2009 – 2015

Deary, Corley et al. (2009) *British Medical Bulletin*
Corley et al. (2009) *Intelligence*
Corley et al. (2015) *British Journal of Nutrition*

APPENDIX C LBC1936 study ethics approval for Wave 1 (2004-2007)

APPENDIX D LBC1936 recruitment flowchart for wave 1 (2004-2007)

APPENDIX E LBC1936 participant information for Wave 1 (2004-2007)

Participant invitation letter sent by Lothian Health Board
Participant information sheet at wave 1
Participant appointment letter to attend assessment at wave 1
Participant consent form at wave 1
Participant questionnaire letter at wave 1

APPENDIX F LBC1936 phenotype collection at wave 1

APPENDIX G Food frequency questionnaire version 7.0

APPENDIX H Scree plots for the cognitive factors

**Appendix A - Publications Submitted for PhD by Research
Publications**

Caffeine Consumption and Cognitive Function at Age 70: The Lothian Birth Cohort 1936 Study

JANIE CORLEY, MA, XUELI JIA, PhD, JANET A. M. KYLE, PhD, ALAN J. GOW, PhD, CAROLINE E. BRETT, MSc, JOHN M. STARR, MA, FRCPE, GERALDINE McNEILL, PhD, AND IAN J. DEARY, PhD, FRCPE

Objective: To investigate the association between caffeine consumption and cognitive outcomes in later life. **Methods:** Participants were 923 healthy adults from the Lothian Birth Cohort 1936 Study, on whom there were intelligence quotient (IQ) data from age 11 years. Cognitive function at age 70 years was assessed, using tests measuring general cognitive ability, speed of information processing, and memory. Current caffeine consumption (using multiple measures of tea, coffee, and total dietary caffeine) was obtained by self-report questionnaire, and demographic and health information was collected in a standardized interview. **Results:** In age- and sex-adjusted models, there were significant positive associations between total caffeine intake and general cognitive ability and memory. After adjustment for age 11 IQ and social class, both individually and together, most of these associations became nonsignificant. A robust positive association, however, was found between drinking ground coffee (e.g., filter and espresso) and performance on the National Adult Reading Test (NART, $p = .007$), and the Wechsler Test of Adult Reading (WTAR, $p = .02$). No gender effects were observed, contrary to previous studies. Generally, higher cognitive scores were associated with coffee consumption, and lower cognitive scores with tea consumption, but these effects were not significant in the fully adjusted model. **Conclusions:** The present study is rare in having childhood IQ in a large sample of older people. The results suggest that the significant caffeine intake-cognitive ability associations are bidirectional—because childhood IQ and estimated prior IQ are associated with the type of caffeine intake in old age—and partly confounded by social class. **Key words:** caffeine, cognitive function, childhood IQ, aging.

BMI = body mass index; **FFQ** = Food Frequency Questionnaire; **MHT** = Moray House Test; **PCA** = Principal Components Analysis; **SMS1947** = Scottish Mental Survey 1947; **LBC1936** = Lothian Birth Cohort 1936; **SES** = socioeconomic status; **NART** = National Adult Reading Test; **WTAR** = Wechsler Test of Adult Reading.

INTRODUCTION

By late adulthood, people typically experience some deterioration in cognitive abilities as part of the normal course of aging. Abilities, such as memory, reasoning, and processing speed, all decline, on average, with age (1). However, there are large individual differences in age-related cognitive changes and it is a research priority to identify factors that affect the rate of age-related cognitive decline. In the setting of an increasingly aged population, such knowledge can improve the health and well-being of older people in the future (2).

There is growing evidence from epidemiological studies that caffeine consumption is associated with better cognitive performance in later life. Caffeine is widely consumed in Western societies, primarily in coffee and tea but also in chocolate and carbonated drinks. It acts as a psychoactive stimulant and has been shown to improve cognitive performance in the short term (3). By increasing the activity of the

central nervous system, caffeine consumption can result in heightened alertness, vigilance, attention, and mood as well as improved complex, higher cognitive functions including memory (4,5). Besides these short-term effects, there is also a growing body of evidence from studies indicating that the habitual consumption of coffee and tea has long-term beneficial effects on brain function (6). Using data from the Health and Lifestyle Survey (HALS), a large cross-sectional study of 9003 British adults, Jarvis (7) reported a dose-response trend between habitual tea and coffee consumption and cognitive performance in all four tasks measured: simple reaction times, choice reaction times, incidental verbal memory, and visuospatial reasoning. Interestingly, the oldest men and women seemed to benefit most from a higher caffeine intake.

One possible explanation, underlying the positive association between caffeine and cognitive abilities in older adults, and adopted by many researchers, is that regular caffeine consumption enhances the neuroprotective actions of adenosine. Like alcohol, caffeine readily crosses the blood-brain barrier. It is well documented that, once in the brain, caffeine acts as an antagonist on the A_{2A} adenosine receptors. By counteracting adenosine, caffeine has a disinhibitory effect, causing the stimulation of cholinergic neurotransmitters (8). These neurotransmitters exert a protective effect against β amyloid-induced neurotoxicity, a precursor to cognitive decline in humans (9) and in mice (10). Caffeine, especially coffee, is rich in biologically active substances, such as polyphenols and antioxidants, and is capable of increasing plasma antioxidant capacity in humans (11). Therefore, another potential physiological mechanism by which caffeine may afford some protection against brain aging is by counteracting the oxidative stress involved in the pathogenesis of aging-related diseases. Another risk factor for cognitive decline is Type II diabetes (12). A systematic review of several large-scale, prospective studies (13) supported the hypothesis that habitual coffee consumption is associated with a substantially lower risk of Type II diabetes. Others have reported protective

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CAFFEINE AND COGNITIVE FUNCTION IN OLD AGE

effects of long-term caffeine intake on the risk of developing Alzheimer's disease (14,15). Coffee drinkers are reported to have a 30% lower risk of developing Parkinson's disease (16).

In recent years, evidence has generally supported the assertion that caffeine intake (particularly from coffee) may help to maintain cognitive functions in aging. Some longitudinal studies have documented an inverse association between coffee consumption and cognitive decline. In a men-only study, Gelder et al. (17) found that, among the elderly, those who drank coffee had half the 10-year cognitive decline than noncoffee drinkers. The least decline occurred for men consuming three cups of coffee per day. Others have reported gender-specific benefits of caffeine on cognitive function favoring women. In a large prospective study, women who drank more than three cups of coffee per day showed less decline in verbal cognitive functioning and visuospatial memory over a 4-year period than women who had low or no consumption of coffee (18). However, no effect was observed in men. Similarly, Johnson-Kozlow et al. (19) reported that lifetime and current exposure to coffee was associated with better cognitive performance among women, but not in men. Female coffee drinkers (especially those aged ≥ 80 years) performed better on cognitive tasks of memory, attention, and concentration. Although men consumed more caffeine than women per day, they hypothesized that women are more sensitive to the pharmacological effects of caffeine than men.

However, some have investigated the relationship between caffeine and cognitive abilities with inconsistent results. Van Boxtel et al. (20) found no significant reduction in age-related cognitive decline with habitual caffeine intake (from tea and coffee) after 6 years and concluded that the longitudinal effect of caffeine is limited at best. Methodological differences may, in part, account for the discrepancies between studies. Tea and coffee consumption is frequently measured as "number of cups consumed daily," whereas others measure caffeine intake based on standard estimations of caffeine per cup of coffee or tea. However, caffeine content can vary markedly between different types of beverages. One cup of instant coffee can contain between 21 mg and 120 mg of caffeine, whereas the equivalent serving size of ground coffee (filter, espresso, etc.) can contain up to 254 mg (21). Assuming that every cup of coffee contains an equivalent level of caffeine is unlikely to give an accurate reflection of caffeine intake. Few studies have included tea consumption in their investigations and no other study, as far as we are aware, has included the effects of overall dietary caffeine exposure on cognitive function, especially in old age.

Attempting to measure the effects of caffeine (or any variable for that matter) on cognitive abilities in old age is problematic without some measure of prior cognitive ability as a baseline comparison. If there is a significant association in a group of older people between caffeine intake and cognitive ability, this does not necessarily mean that caffeine is beneficial for cognitive abilities in old age. One of the limitations of most studies in the field of cognitive aging is the possibility of reverse causation; that is, the supposed depen-

dent (outcome) variable might be causing changes in the supposed independent (predictor) variable. It is possible that early life intelligence influences caffeine intake as well as vice versa. It is well demonstrated in large, population-representative samples that childhood intelligence quotient (IQ) influences many aspects of diet and health-related life-style (22). The Lothian Birth Cohort 1936 (LBC1936) is almost unique in terms of having a measure of IQ at both childhood (age 11 years) and later life (age 70 years) in addition to multiple cognitive domain scores and demographic and health data from late life. This data set is in an ideal position to provide an insight into the associations, if any, between caffeine intake and cognition in older people. The aim of the present study was to examine the association between caffeine consumption (coffee, tea, and additional sources) and performance on a comprehensive battery of cognitive function tests in a sample of older adults (aged about 70 years) from the LBC1936 study, at the same time controlling for prior cognitive ability (age 11 IQ). Cognitive assessment at age 70 years included multiple markers of memory, speed of information processing, general cognition, and verbal intelligence. Focusing on these specific cognitive domains may help to untangle the effects of caffeine on cognitive performance in older adults.

METHODS

Participants and General Methods

The participants were surviving participants of the Scottish Mental Survey of 1947 (SMS1947) (23). The SMS1947 tested the mental ability of almost all Scottish schoolchildren born in 1936 and attending school on June 4th 1947 (aged 11 years), using a well-validated test of general intelligence: a version of the Moray House Test (MHT) No. 12. The 1091 surviving participants described in the present study are known as the LBC1936. Full details of the recruitment and testing of the LBC1936 are given in a free-access protocol paper (24). At the time of recruitment, LBC1936 members mostly resided in Edinburgh and its surrounding area (Lothian) in Scotland. They were relatively healthy and lived independently. Between July 2004 and May 2007, at a mean age 69.5 years, each LBC1936 participant attended the Wellcome Trust Clinical Research Facility at the Western General Hospital in Edinburgh to undergo extensive cognitive and physical testing and an interview. Cognitive assessments were conducted by trained researchers and physical testing was carried out by research nurses. The standardized interview ascertained demographic information, smoking and alcohol consumption, medical history, and medication use. As a part of their general assessment, LBC1936 participants were asked to complete the Scottish Collaborative Group 165-item Food Frequency Questionnaire (FFQ) (25). Ethics permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee (LREC/2003/2/29). The research was carried out in compliance with the Helsinki Declaration. All participants gave their written, informed consent.

Procedure

Measurement of Caffeine Intake

Caffeine intake was assessed, using the Scottish Collaborative Group FFQ, version 7.0 (25). The FFQ has been found to have good repeatability (dietary intake in later life is reasonably stable in the short term) and good validity for most nutrients in community-dwelling older populations (26–28). This self-report questionnaire comprises questions about dietary intake over the previous 2- to 3-month period and is designed to estimate daily intake of a wide range of nutrients. The FFQ measures intake of caffeine from the main dietary sources, namely, "instant coffee" (freeze-dried), "filter, espresso or

cappuccino coffee" (hereby collectively referred to as "ground coffee"), "decaffeinated coffee," "tea (regular)," "herbal, fruit, or decaffeinated tea," "diet fizzy drinks (cola, lemonade, etc.)," "regular fizzy drinks," "hot chocolate," "Horlicks or Ovaltine," "mousse, blancmange, trifle, meringue," "chocolate bars (e.g., Mars, Dairy Milk)," "chocolate sweets, toffees, or fudge," "chocolate coated biscuits," "peanut butter or chocolate spread." Each item on the questionnaire refers to a standard measure, e.g., 1 cup or mug (hot drinks), 1 biscuit, 1 can (fizzy drinks). Participants mark one of nine responses to indicate frequency of consumption of the measure: rarely or never; 1 to 3 per month; 1 per week; 2 to 3 per week; 4 to 6 per week; 1 per day; 2 to 3 per day; 4 to 6 per day; 7 + per day.

The FFQ was given at the clinic visit and returned in a stamped addressed envelope. In the event of any missing responses, a letter was sent requesting the information. If there were >10 missing items (even after a letter had been sent), the FFQ was labeled "incomplete" and excluded from the analyses. A total of 929 participants (85%) returned completed (<10 missing items) questionnaires (51.6% by women). A total of 97 questionnaires were not returned, 26 were returned blank, 39 were incomplete. One "completed" questionnaire had several missing caffeine-containing items and was excluded. Five additional individuals were excluded because they were identified as having potential dementia based on a score of <24 on the Mini-Mental State Examination (MMSE) (29). Therefore, the final sample for analysis in the present study comprised 923 relatively healthy participants ($n = 446$ men, 477 women) aged about 70 years (mean = 69.5, standard deviation = 0.8) at time of testing.

The amount of caffeine (coded as milligrams daily) estimated to be present in each item was calculated, using a caffeine composition database compiled from British beverage and food caffeine surveys, where caffeine levels were obtained using validated analytical techniques (21,30–35). Estimated average caffeine values were assigned to each food or drink including (per 1 cup or mug serving) tea (34.2 mg), instant coffee (43.7 mg), and ground coffee (93.1 mg). A measure of "total caffeine" consumption was derived from all 14 caffeine-containing items in the FFQ. To investigate the effect of overall coffee intake, because this is often used in the previous literature, an additional measure of "total caffeine from coffee" was derived by combining consumption of both instant coffee and ground coffee.

Measurement of Cognitive Performance at Age 70

A full description of the cognitive tests and administration procedures used can be found in the free-access LBC1936 protocol article (24). Cognitive testing was carried out by a trained researcher. Brief descriptions of the tests follow.

The MMSE was used as a screening measure for cognitive pathology (29). Scores range from 0 to 30, with a score of <24 indicating possible dementia.

From the Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III) (36), we included: Digit Symbol Coding (speed of information processing); Block Design (constructional ability); Matrix reasoning (nonverbal reasoning); Digit Span backwards (working memory); Symbol Search (speed of information processing); Letter-number sequencing (working memory).

From the Wechsler Memory Scale-III^{UK} (WMS-III) (37), we used: Logical Memory I and II (verbal declarative memory, immediate and delayed recall); Verbal Paired Associates I and II (verbal learning and memory, immediate and delayed recall); Spatial Span (nonverbal spatial learning and memory).

Verbal Fluency (phonemic) provides a measure of executive function (38). National Adult Reading Test (NART) (39) and Wechsler Test of Adult Reading (WTAR) (40) are widely used to estimate prior cognitive ability and they require the pronunciation of irregular words. Simple and Four-choice reaction time measure speed and variability of simple information processing, using a purpose-built portable machine (41,42). Inspection time is a computer-based task used to assess speed of elementary visual processing (43).

Demographic and Control Variables Including Childhood IQ

Demographic and medical information was obtained at the clinic assessment. During the standardized interview, participants were asked questions relating to their marital status, education (number of years of full time [F/T]

education), current alcohol consumption (type and frequency, from which units per week were calculated), and smoking status (current, ex-, or never smoker). Social class was derived from participants' highest reported occupation (44) and consisted of six categories ranging from I (professional occupations) to V (unskilled occupations), with III (skilled occupations) divided into IIIN (nonmanual) and IIIM (manual). The women in the cohort were asked for their husband's occupation as well as their own, and they were assigned a social class based on the highest occupation of the household. This was derived from their own occupation for about half of the women, and from their husband's occupation for the remainder. Social class is here represented in a numeric fashion with classes IIIN and IIIM expressed as 3 and 3.5, respectively, to reflect their relative status. A detailed medical history was taken (including diagnoses of diabetes, high blood pressure, and high cholesterol). Anxiety and depression symptoms were assessed, using the Hospital Anxiety and Depression Scale (HADS)—a short self-assessment scale consisting of seven items for anxiety and seven for depression. A physical examination was performed by a nurse including measurements of height and weight, from which body mass index (BMI) was calculated. Participants completed a 20-page questionnaire booklet containing various social and life-style questionnaires and measures of physical activity (including number of days per month of exercise).

Age 11 scores were obtained, in collaboration with the Scottish Council for Research in Education (SCRE) and with the permission of LBC1936 participants, from the original SMS1947 records. The MHT No.12 was taken by participants in the SMS1947 at age 11 (45) and repeated at their clinic visit at about age 70. MHT scores were corrected for age in days at time of testing and converted to standard IQ type scores, where mean = 100 and SD = 15. This is a well-validated general mental test comprising 71 items (mostly verbal reasoning, but also some numerical, spatial, and other items) with a maximum score of 76 and a 45-minute time limit.

Statistical Analyses

Demographic and health differences between tertiles of caffeine intake groups were examined, using analysis of variance (ANOVA), χ^2 and t tests as appropriate. Tertiles of consumption were used for illustrative purposes only; the main analyses were conducted, using caffeine as a continuous variable. Associations between caffeine consumption (derived from total caffeine, tea, instant coffee, ground coffee, and total coffee) and cognitive function were examined, using univariate general linear models. Four models were fitted to the data, each including adjustment for potential confounding factors. The base model included age (in days at time of testing) and sex. The second model included age, sex, and occupational social class. A third model included age, sex, and age 11 IQ to control for early-life cognitive ability. In the fourth and final model, all four control variables were included. A general cognitive ability component score (g factor) was derived from principal components analysis (PCA) of six WAIS-III subtests (Letter-number sequencing, Matrix reasoning, Block design, Digit symbol, Digit Span backwards, Symbol search). A general processing speed component score (speed) was similarly derived from a PCA of the set of speed measures (Symbol search, Digit symbol, Simple Reaction Time mean, Choice Reaction Time mean, Inspection time). The extraction of these factors by PCA has been described elsewhere (46). Using the same method, a general memory factor (memory) was extracted from the WMS-III subtests (Logical memory I immediate and II delayed recall, Spatial span forwards, Spatial span backwards, Verbal paired associates I immediate and II delayed recall) and two WAIS-III subtests (Letter-number sequencing, Digit Span backwards). The fourth cognitive outcome variable used in the present study is age 70 IQ (MHT score at age 70 years corrected for age in days at time of testing and converted to an IQ scale, where mean = 100 and SD = 15). Additional analyses were performed with NART and WTAR scores (measures of verbal IQ) as cognitive outcomes. We present estimates of effect size as well as p values.

RESULTS

The characteristics of study participants are presented in Table 1 by tertile of total caffeine consumption; low caffeine (1.2–131.0 mg/day); medium caffeine (131.0–211.0 mg/

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TABLE 1. Characteristics of the Study Population by Category of Daily Caffeine Consumption (Mean Values and % Prevalence)

	Total Sample <i>n</i> = 923 ^a		Low Caffeine <i>n</i> = 302		Medium Caffeine <i>n</i> = 303		High Caffeine <i>n</i> = 302		<i>p</i>
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Caffeine (mg/day)	182.5	97.8	85.5	34.3	175.0	22.8	287.2	81.1	
Age (years)	69.5	0.84	69.6	0.83	69.5	0.85	69.4	0.84	.30
Sex									.24
Male (%)	48.3		51.0		50.2		44.7		
Female (%)	51.7		49.0		49.8		55.3		
Marital status									.10
Married (%)	72.4		67.9		72.3		77.2		
Widowed (%)	13.3		14.9		14.1		10.9		
Unmarried/divorced (%)	14.2		16.9		13.5		11.8		
Education (years F/T)	10.8	1.2	10.7	1.1	10.8	1.1	10.9	1.3	.10
MMSE	28.9	1.2	28.8	1.3	29	1.2	29	1.2	.18
Alcohol consumption (units/wk)	10.6	14.3	11.6	18.2	9.9	12.2	10.1	11.4	.27
BMI (kg/m ²)	27.6	4.3	28.1	4.1	27.4	4.1	27.4	4.5	.08
Physical activity (days/mo.)	7.5	8.0	7.0	7.6	8.0	8.2	7.7	8.3	.33
Smoking status									.29
Nonsmokers (%)	44.4		43.0		47.5		42.1		
Ex-smokers (%)	43.2		47.0		40.6		43.0		
Current smokers (%)	12.4		9.9		11.9		14.9		
Hypertension, yes (%)	39.5		47.0		38.6		33.1		.002
Diabetes, yes (%)	7.5		11.3		6.3		5.0		.008
Cholesterol, yes (%)	35.1		39.7		35.8		29.5		.03

SD = standard deviation; F/T = full time; MMSE = Mini-Mental State Examination; BMI = body mass index; mo. = month.

The *p* values are from *t* tests, analysis of variance, and χ^2 tests as appropriate.

^a Full study sample comprises 923 men and women. Due to some missing caffeine data, 16 subjects have no total caffeine measure and, therefore, are not included in the tertiles of consumption.

day); high caffeine (211.0–701.1 mg/day). Of the 923 participants who provided caffeine data, data from 16 cells were incomplete (no more than one incomplete caffeine item per person). Analyses were conducted on caffeine data from all 923 FFQs; however, total caffeine was calculated only where data were complete (*n* = 907). High-caffeine consumers were significantly less likely to have had a diagnosis of high blood pressure (*p* < .001), diabetes (*p* = .005), or cholesterol (*p* = .008) than low-caffeine consumers. Medium-caffeine consumers were significantly less likely to have had a diagnosis of high blood pressure (*p* = .04) or diabetes (*p* = .03) than low-caffeine consumers. Level of caffeine consumption was not significantly associated with any other demographic variable. Nonresponders to the FFQ (where questionnaires were not returned or returned blank, *n* = 123) were significantly more likely to be men than women (*n* = 74 versus 49, χ^2 (1) = 5.47, *p* = .02), have less years of F/T education (mean = 10.52 versus 10.77, *p* = .02) and lower MMSE scores (mean = 28.3 versus 28.9, *p* < .001) than responders. Responders and nonresponders differed significantly in their smoking status (χ^2 (2) = 6.192, *p* = .04).

Total Caffeine

Mean total caffeine intake (per day) from all dietary sources was 182.5 mg, and ranged from 1.2 mg to 701.1 mg (Table 2). Caffeine intake (mean) was slightly higher in

women (187.9 mg) than men (176.8 mg), although this difference was nonsignificant.

Caffeinated Tea/Coffee

Coffee and tea consumption in this Scottish cohort was widespread. A total of 97.7% of participants reported consuming caffeinated tea or coffee in the last 2 to 3 months. Twenty-one participants (2.3%) reported that they “rarely or never” drank caffeinated tea or coffee. Of the total sample, 85.5% consumed tea, 72.0% consumed instant coffee, and 49.0% consumed ground coffee (Table 2). Women consumed significantly more ground coffee than men; otherwise, there were no statistical differences between the consumption of different types of caffeinated tea or coffee by gender. Beverage preference did not seem to be exclusive; 84% of the sample drank both tea and coffee. However, as expected, there was a significant negative correlation between tea and coffee consumption (−0.28, *p* < .001), suggesting that heavy consumers of tea tend to drink little coffee and vice versa.

Decaffeinated Tea/Coffee

Men and women differed significantly in their consumption of decaffeinated tea and coffee. Compared with men, women had a significantly higher mean intake of decaffeinated tea (*p* < .001) and decaffeinated coffee (*p* = .001) (data not presented). In this older cohort, consumption of decaffeinated

TABLE 2. Caffeine Consumption in Men and Women (Median Values, Ranges, and *p* Values) and Correlations With Age 11 Intelligence Quotient (IQ) and Social Class

Caffeine (mg/day)	Total Sample <i>n</i> = 923			Men <i>n</i> = 446			Women <i>n</i> = 477			Mann-Whitney <i>U</i> <i>U</i> (<i>p</i>)	Age 11 IQ Spearman rho <i>r_s</i> (<i>p</i>)	Social Class Spearman rho <i>r_s</i> (<i>p</i>)
	Median (Range)	% Reporting		Median (Range)	% Reporting		Median (Range)	% Reporting				
Total caffeine (all sources) ^a	177.5 (0–701.1)			175.7 (12–563.2)			178.1 (7.0–701.1)			97406.5 (.18)	0.053 (.12)	–.098 (.003)
Caffeine from tea (regular)	85.5 (0–256.5)	85.5		85.5 (0–256.5)	87.6		85.5 (0–256.5)	83.4		103064.5 (.47)	–0.113 (.001)	.067 (.04)
Caffeine from instant coffee	43.7 (0–327.8)	72.0		43.7 (0–327.8)	75.2		31.0 (0–327.8)	68.8		98315.5 (.08)	0.034 (.32)	.042 (.21)
Caffeine from ground coffee	0 (0–698.3)	49.0		0 (0–465.5)	44.6		6.5 (0–698.3)	52.6		97022.0 (.01)	0.236 (<.001)	–.277 (<.001)
Total caffeine from coffee	50.2 (0–698.3)			50.2 (0–465.5)			50.2 (0–698.3)			104849.0 (.92)	0.159 (<.001)	–.154 (<.001)

^a Due to some missing caffeine data, 16 subjects have no total caffeine measure.

coffee and herbal tea was insufficient to warrant inclusion in the analyses as separate measures of caffeine consumption. Although they contribute relatively small amounts of caffeine to the diet and were consumed by less than a quarter of our sample, they are included in the “total caffeine” measure (Table 2).

Caffeine Consumption, Age 11 IQ, and Social Class

Age 11 IQ and social class were identified as potential confounding variables of an association between caffeine intake and cognitive ability at age 70. There were significant positive correlations between age 11 IQ score and caffeine from ground coffee and total coffee, and a significant negative correlation with tea (Table 2). There were significant negative correlations between social class group (where a lower number indicates a more professional occupation) and total caffeine, caffeine from ground coffee, total coffee, decaffeinated coffee, and herbal/other tea and a significant positive correlation with tea. There was a general trend for increasing (caffeinated) tea consumption in the lower social class groups and those with lower age 11 IQ scores; and there was generally higher coffee consumption in higher social class groups and those with higher age 11 scores.

Caffeine Consumption and Cognitive Performance at Age 70

Table 3 displays the results of four univariate general linear models for each cognitive outcome variable. Examination of models including appropriate interaction terms revealed no significant effects of caffeine by gender. Results are therefore not differentiated by gender below, and interactions were not included in the final models.

The overall caffeine measure “total caffeine” was significantly and positively associated with memory (in the base model only) and with age 70 IQ, NART, and WTAR in the base model and model 3 (with age 11 IQ) but not after social class adjustment or in the fully adjusted model. Caffeine from tea had a significant, inverse association with age 70 IQ, *g* factor, processing speed, NART and WTAR scores in model 1 (sex and age adjusted, *p* < .01) and model 2 (sex, age, and social class adjusted, *p* < .05). However, when age 11 IQ was added (as in models 3 and 4), all significant associations fell to nonsignificant levels. The memory factor was not found to be associated with this caffeine measure. Results indicated no relationship between caffeine from instant coffee and cognitive test scores at age 70 at any stage in the analyses. Caffeine from ground coffee was significantly associated with better performance on all age 70 cognitive measures (age 70 IQ, *g* factor, processing speed, memory, NART, and WTAR, *p* < .001) but this was found in the baseline model only, with the exception of processing speed, NART, and WTAR. The association with processing speed was attenuated with the addition of age 11 IQ; then, it declined to nonsignificant levels when social class was included (models 2 and 4). The association with NART and WTAR scores, however, not only retained significance when controlling for age 11 IQ but

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TABLE 3. Associations Between Caffeine Intake and Cognitive Outcomes

Predictor mg per day	Model	Age 70 IQ <i>n</i> = 919		<i>g</i> Factor <i>n</i> = 909		Processing Speed <i>n</i> = 887		Memory <i>n</i> = 893		NART <i>n</i> = 923		WTAR <i>n</i> = 923	
		<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2
Total caffeine (all sources)	1	.03 ^b	0.005	.05	0.004	.27	0.001	.02 ^b	0.007	.01 ^b	0.007	.02 ^b	0.006
	2	.35	0.001	.47	0.000	.93	0.000	.13	0.003	.29	0.001	.33	0.001
	3	.04 ^b	0.005	.14	0.003	.36	0.001	.05	0.004	.02 ^b	0.007	.02 ^b	0.006
	4	.12	0.003	.44	0.000	.90	0.000	.11	0.003	.14	0.003	.16	0.002
Caffeine from tea	1	<.001 ^c	0.012	<.001 ^c	0.014	.001 ^c	0.013	.20	0.002	.002 ^c	0.011	.007 ^c	0.008
	2	.006 ^c	0.008	.003 ^c	0.010	.002 ^c	0.011	.39	0.000	.01 ^c	0.007	.03 ^c	0.005
	3	.62	0.000	.26	0.001	.08	0.004	.37	0.000	.68	0.000	.97	0.000
	4	.74	0.000	.30	0.001	.06	0.004	.38	0.000	.70	0.000	.99	0.000
Caffeine from instant coffee	1	.07	0.004	.30	0.001	.16	0.002	.29	0.001	.94	0.000	.98	0.000
	2	.06	0.004	.25	0.002	.21	0.002	.28	0.001	.80	0.000	.93	0.000
	3	.19	0.002	.78	0.000	.34	0.001	.75	0.000	.31	0.001	.25	0.002
	4	.21	0.002	.72	0.000	.39	0.001	.73	0.000	.42	0.000	.29	0.001
Caffeine from ground coffee	1	<.001 ^b	0.014	<.001 ^b	0.017	<.001 ^b	0.001	<.001 ^b	0.014	<.001 ^b	0.033	<.001 ^b	0.028
	2	.15	0.002	.08	0.003	.06	0.004	.05	0.004	.002 ^b	0.011	.005 ^b	0.009
	3	.20	0.002	.05	0.004	.03 ^b	0.006	.11	0.003	<.001 ^b	0.018	<.001 ^b	0.014
	4	.49	0.000	.38	0.000	.16	0.002	.25	0.002	.007 ^b	0.008	.02 ^b	0.007
Total caffeine from coffee	1	<.001 ^b	0.018	<.001 ^b	0.016	<.001 ^b	0.015	<.001 ^b	0.014	<.001 ^b	0.021	<.001 ^b	0.017
	2	.01 ^b	0.007	.03 ^b	0.005	.02 ^b	0.006	.02 ^b	0.006	.008 ^b	0.008	.02 ^b	0.006
	3	.05	0.004	.08	0.003	.02 ^b	0.007	.14	0.003	.01 ^b	0.007	.05	0.004
	4	.15	0.002	.34	0.001	.09	0.004	.24	0.002	.12	0.003	.26	0.002

IQ = intelligence quotient; NART = National Adult Reading Test; WTAR = Wechsler Test of Adult Reading.

General linear models, *p* values, and associated partial eta squared values. Model 1: sex+age; Model 2: sex+age+social class; Model 3: sex+age+age 11 IQ; Model 4: sex+age+age 11 IQ+social class.

^a Age 70 IQ is already age-adjusted (age not included in the models for this outcome variable).

^b Denotes a positive model correlation coefficient.

^c Denotes a negative model correlation coefficient.

survived full adjustment for all covariates ($p = .007$ and $p = .02$, respectively). Additional adjustment for years of F/T education further attenuated this association but did not remove it ($p = .02$, $\eta_p^2 = 0.006$; $p = .04$, $\eta_p^2 = 0.005$, respectively). Education correlates strongly with age 11 IQ in this sample (0.382 , $p < .001$) and explains less of the variance in age 70 IQ than age 11 IQ. For this reason, we do not present the results, using education as a confounder. Caffeine from total coffee (a measure often used in the literature) had a significant, positive association with all age 70 cognitive measures, using the base model ($p < .001$). Unlike caffeine derived from ground coffee only, the associations between this combination coffee measure and all five cognitive outcome variables remained significant when controlling for social class. However, these associations were either attenuated (processing speed, NART) or declined to nonsignificance once age 11 IQ scores are included in the model. None of the associations survive the fully adjusted model.

DISCUSSION

The results provide limited support for a positive effect of caffeine consumption on cognition in later life. There are three main results of interest. First, after adjustment for childhood IQ, most of the “protective” effects of caffeine on cognition are removed. Previous studies reporting beneficial effects of caffeine (or coffee) consumption on cognitive function in old age have been unable to control for prior ability. IQ is rela-

tively stable over time (47,48). In this sample, the correlation between age 11 IQ and age 70 IQ is 0.66 ($p < .001$), supporting the assertion that childhood IQ accounts for the majority of variance in later-life cognition. The remaining variance is accounted for by factors other than caffeine intake. With full adjustments for age, sex, social class, and age 11 IQ, we found no protective effects of caffeine consumption on performance on memory, speed of information processing, or general cognition component scores and on the MHT (a general intelligence test) at age 70.

Second, the only indication that caffeine consumption exerts a protective influence on cognitive performance was that drinkers of ground (filter and espresso type-) coffee performed better on tests of verbal intelligence (NART and WTAR) than nondrinkers of ground coffee, even when controlling for age 11 IQ and social class. Performance on these tests is widely assumed to reflect prior cognitive ability and level of education. Highly significant, positive correlations exist between age 11 IQ and NART and WTAR scores (0.66 , $p < .001$; 0.64 , $p < .001$, respectively) in this population. For this reason, it was initially surprising that there remained a beneficial effect of ground coffee intake on performance on these tests, once age 11 IQ has been controlled for. However, NART and WTAR are thought to capture peak, prior adult cognitive ability. Perhaps the association between ground/espresso coffee drinking and NART and WTAR is still significant after adjusting for age 11 IQ because they capture variance related

to intellectual development and its associated education and life-style choices between childhood and adulthood.

Third, even before controlling for age 11 IQ, no gender effects were found, contrary to previous studies. Many have reported effects of caffeine on cognition in women, but not men. However, patterns of consumption differ widely as a result of cultural habits. Much of the caffeine research reporting gender effects comes from cohorts in the Netherlands and Finland, which are known for being heavy-caffeine (predominantly coffee) consumers with an average daily caffeine intake of 400 mg per day in both men and women (49). The results of these studies may not be generalizable to the United Kingdom, where survey data revealed that average consumption was a more moderate 240 mg per day. The Bristol Dietary Caffeine and Health Study surveyed 5870 British adults and found that caffeine intakes were significantly higher in men (263 mg/day) than in women (226 mg/day) (50). However, in the present study, the average age was older (at 70 years). Mean daily caffeine intake was lower (182 mg/day) than the UK average and comparable in men and women. This is not surprising, given that caffeine (especially coffee) intake decreases with age, especially after about 65 years. Coffee has significantly higher concentrations of caffeine and more stimulating effects than tea. Because there is a greater sensitivity to the effects of caffeine in older people, tea may become the beverage of choice. Perhaps any prior difference in caffeine consumption (and its effects) by gender disappears with increasing age. It is nevertheless surprising that, given the very narrow age range in this cohort (all born in 1936), there was a (nonsignificant) trend for the high-caffeine consumers to be younger than both medium- and low-caffeine consumers.

Throughout the models, there was a general trend for individuals who drink more coffee and less tea to have better cognitive health at age 70, but these effects were not borne out statistically by our analyses. Previous studies have attributed the opposing effects of tea and coffee on health outcomes, either to differing “pharmacological” effects of tea and coffee or to life-style or socioeconomic differences between the consumers of these beverages (51,52). In Scotland, research suggested that coffee drinking is associated with higher socioeconomic status (SES) and good health, whereas drinking tea is associated with lower SES and poorer health outcomes (53). The present study supports, in part, these research findings; in the LBC1936, tea consumption was higher in the “lower” social classes, whereas those who drink coffee were more likely to belong to the “higher” social classes. However, the more important confounder in this study was age 11 IQ (with some contribution from social class). The results of the general linear models suggest that it is age 11 IQ which is driving most of the associations with performance on cognitive tasks at age 70 years. Individuals with a high childhood IQ at age 11 were more likely to continue to perform better into adulthood than those with a lower age 11 IQ, irrespective of their caffeine intake. Age 11 IQ was also predictive of tea or total coffee intake in late life; higher IQ children were more likely to drink coffee, whereas poorer performance on the age

11 test was linked with a preference for tea some 60 years later. These findings suggest a bidirectional relationship between type of caffeine intake and IQ.

We conducted a post hoc mediational analysis (Sobel test) to examine the extent to which the age 11 IQ and coffee intake at age 70 association is mediated by social class. The standardized beta of the direct path (age 11 IQ-ground coffee consumption) was 0.132, and 0.054 after social class was introduced as a mediator. The amount of the relationship between age 11 IQ and ground coffee consumption, accounted for by social class as a mediator, was 0.08; this represents 59.1% of the direct effect ($z = 5.27, p < .001$). Rather than suggesting a causal link between early-life ability and adult tea or coffee preference, the results may reflect the fact that those individuals with a higher childhood IQ are more likely to achieve a higher SES and may, therefore, be more represented in social groups that choose to follow a life-style that is more “cosmopolitan.” This would be reflected in social and dietary preferences. Coffee drinking, in the United Kingdom, is associated with an urban life-style among both young- and older-educated individuals. Therefore, the association between adult cognitive ability and tea and coffee consumption may simply be reflecting life-style preferences that vary with IQ/SES.

Further support for this alternative explanation may arise from the finding that caffeine consumption in our cohort was associated with a range of health outcomes also associated with cognitive decline. We found less evidence of markers of ill health in the high-caffeine group than the low-caffeine group. Men and women with the highest consumption of caffeine were less likely to have ever had diabetes, high blood pressure, and high cholesterol than those drinking less caffeine. This contradicts prevailing medical opinion that caffeine has adverse effects on health but supports, to a certain extent, the findings of the Scottish Heart Health Study (53); they reported that in Scotland coffee drinking was associated with a reduction in coronary risk factors, coronary risk, and mortality, and that the converse was true of tea.

One of the advantages of this study is that we have used a uniformly older cohort who share the same year of birth. We were able to control for a range of demographic variables, which have previously been related to caffeine intake. Second, we were able to investigate the effects of drinking different types of coffees as well as measuring total caffeine consumption from a wide variety of dietary sources, not just tea and coffee. Third, using general cognitive factors (extracted from the large cognitive test battery), we were able to investigate the effects of caffeine on different aspects of cognitive function. Fourth, we had a measure of childhood IQ. There will be opportunities for follow-ups of this cohort offering the potential to investigate caffeine's effects on cognitive decline.

Selective attrition could have contributed to a healthy survivor effect. One potential limitation of the study is that the sample represents a healthy and high-functioning subgroup of the SMS1947 cohort. Our sample achieved higher mean age 11 IQ scores (mean = 50.02, SD = 11.04) than the original

cohort (mean = 36.74, SD = 16.10), and this may have restricted the range of cognitive outcome scores. The range of age 11 IQ scores in the sample was large. The most likely result of this is some small underestimation of effect sizes of the associations. Further limitations of the study concern the measurement of caffeine. FFQ responses reflect the previous 2- to 3-month period only. Current intake was assumed to be representative of habitual intake, as diet (including tea and coffee consumption) is likely to remain stable over time (barring illness). We cannot exclude the possibility that some people may have significantly altered their caffeine intake after a diagnosis or period of bad health. Medical advice often dictates that coffee intake should be kept to a minimum, especially in the presence of high blood pressure and vascular problems.

Caffeine levels in this study are estimations only, based on the best available government survey data, and are not comparable to the experimental caffeine studies, which are laboratory based. Using estimated measures of caffeine content in drinks is problematic. Caffeine intake estimates may be limited by the high variability in caffeine composition of foods and beverages. In theory, ground coffee has a higher caffeine content than instant coffee and making this distinction during data collection is important. However, a weak ground coffee may be equivalent in caffeine strength to a strong instant coffee. The effects found in this Scottish sample may not be generalizable to other populations. Tea drinking is the norm in the United Kingdom, where there is a higher annual per capita tea consumption than any other country. Even by today's standards, drinking filter and espresso coffee is associated with an educated, middle class life-style. In many other countries, consumption of strong, ground coffee is ubiquitous and independent of social position. Although coffee drinking in the United Kingdom is associated with SES, the mediation analysis, which found that childhood IQ explains more of the variance in adult cognitive ability than social class, provides a clear locus in the present study's findings where there are implications beyond the UK setting.

CONCLUSIONS

The present study provides little evidence that caffeine consumption has protective effects on cognitive function at age 70. It would seem that childhood IQ and other factors including social class, rather than caffeine intake, are driving the association with later-life cognition. This study places childhood IQ and social class firmly within the framework of the diet-cognition relationship and raises doubts about the hypothesized causal effects of long-term caffeine consumption as a protective factor against cognitive decline in later life. However, there may be some residual benefit of drinking ground coffee (typically the stronger types of coffee often consumed in cafes and restaurants) on verbal IQ, irrespective of prior ability. Although these associations are interesting, the contribution of caffeine is very small in relation to other intervening factors. Before advocating the benefits of coffee on cognitive health and general well-being, further research is

needed to fully understand the nature of these associations and rule out chance confounding by other factors.

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Is Body Mass Index in Old Age Related to Cognitive Abilities? The Lothian Birth Cohort 1936 Study

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We tested the hypothesis that the previously reported association between a higher body mass index (BMI) and poorer cognition in later adulthood is an artifact of confounding by previous cognitive ability and socioeconomic status. Participants were 1,079 adults aged about 70 years in the Lothian Birth Cohort 1936 Study, on whom there are IQ data from age 11. Cognitive outcome measures included: IQ at age 70 using the same test that was administered at age 11; composite measures of general cognitive ability (g factor), speed of information processing, and memory; and two tests of verbal ability. People classified as overweight or obese in later adulthood had significantly lower scores on tests of childhood IQ, age 70 IQ, g factor, and verbal ability. There was no significant association with processing speed or memory performance. After adjusting for childhood IQ and social class in general linear models, associations with age 70 IQ and g factor were nonsignificant or attenuated. However, throughout the models, there was a persistent (inverse) relationship between BMI and performance on the National Adult Reading Test (NART) and Wechsler Test of Adult Reading (WTAR), which remained significant after full adjustment for all sociodemographic and health covariates (for the NART, $p = .025$; for the WTAR, $p = .011$). The findings suggest that the previously reported BMI–cognition associations in later adulthood could be largely accounted for by prior ability and socioeconomic status, and by the possible influence of these factors on the adoption of health behaviors in adulthood.

Keywords: body mass index, obesity, cognitive function, childhood IQ, aging.

Overweight and obesity rates are soaring worldwide, even among older adults. Scotland has one of the worst obesity records among developed countries (Organisation for Economic Co-operation and Development, 2007). The Scottish Health Survey of 2008 identified that over two thirds of adults ages 65–74 were either overweight or obese (Gray & Leyland, 2009). The adverse health effects of being overweight at older ages are well estab-

lished and include hypertension, hyperlipidemia, Type II diabetes, and cardiovascular disease (CVD; Brown et al., 2000; Dixon, 2010; Field et al., 2001). Such diseases can lead to early death and significant morbidity in those who survive to old age. In recent years, much scientific research has also been devoted to investigating whether being overweight leads to faster cognitive decline in later life.

Several population-based studies demonstrate an association between overweight and obesity in midlife, commonly defined according to body mass index (BMI), and an increased risk of cognitive impairment in later life (Cournot et al., 2006; Dahl et al., 2009; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003) and dementia (Gorospe & Dave, 2007; Gustafson, Rothernberg, Blenow, Steen, & Skoog, 2003; Kivipelto et al., 2005; Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005; Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007). In a study of healthy, middle-aged men and women, a higher BMI was associated with lower cognitive function at baseline (after adjustment for demographic and health variables) and with greater cognitive decline after a 5-year follow-up period (Cournot et al., 2006). However, the analyses did not adjust for baseline cognitive ability. Given the strong correlation between baseline and follow-up cognitive scores (i.e., the stability of individual differences in cognitive abilities), some doubt must be cast on the longitudinal nature of these and other findings.

Previous reports suggestive of an increased risk of cognitive impairment with a higher BMI are typically based on the effects of BMI measured at midlife. Whereas there is some suggestion that this inverse BMI–cognition relationship does not appear to vary with age (Gunstad et al., 2007), the results from studies examining

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old-age BMI and risk of cognitive impairment are less consistent. Research conducted in some elderly populations appears to show the opposite relationship, where a lower BMI (normal weight) was associated with worse cognition (Kuo et al., 2006; Ng, Feng, Niti, & Yap, 2008; West & Haan, 2009), a faster rate of cognitive decline, and an increased risk of dementia, compared with a higher BMI indicating overweight (Atti et al., 2008; Buchman et al., 2005). Aging is sometimes associated with weight loss, and in the elderly, underweight often precedes clinical evidence of dementia and can be a general marker of ill health (Barrett-Connor, Edelstein, Corey-Bloom, & Wiederholt, 1998; Rosengren et al., 2005; Whitmer et al., 2007). It is clear that the relationship between obesity parameters and cognitive function becomes more complex with age and that there are gaps in the evidence, especially for individuals aged 70 and over without dementia.

The direction of causality typically assumed in many studies is from overweight/obesity to impaired cognition. Several mechanisms, based on the action of biological mediation pathways, have been proposed to account for this effect, including an increased risk of vascular disease (Decarli, 2004), neurochemical changes (Bray, 2004), and brain abnormalities (Gazdzinski, Kornak, Weiner, & Meyerhoff, 2008) with increased adiposity. However, there is increasing evidence, supported by the results of many longitudinal birth cohort studies, that early life cognition is a significant influence on both later life BMI and cognition. It is known that early life intelligence (as assessed by IQ-type tests) accounts for the majority of variance in later life intelligence (Deary, Whalley, Lemmon, Crawford, & Starr, 2000). Furthermore, results from large-scale, longitudinal studies show that a lower childhood IQ score is related to adiposity in adulthood and associated health conditions such as hypertension, CVD, and mortality (Chandola, Deary, Blane, & Batty, 2006). Crucially, intelligence from childhood is also associated with obesity-related health behaviors, such as diet, physical exercise, smoking (Batty, Deary, Schoon, & Gale, 2007; Chandola et al., 2006), and alcohol consumption (Batty, Deary, & Macintyre, 2006; Batty et al., 2008; Mortensen, Sørensen, & Grønbaek, 2005). On the basis of recent epidemiological evidence, Gottfredson (2004) suggested that IQ may be the single, most important factor in the adoption of health behaviors and maintaining a healthy body weight. It is therefore possible that the link between a higher BMI and cognitive impairment in older people may be indirect and explained by a lower intelligence in early life. People with lower childhood IQ test scores are generally more socioeconomically disadvantaged in adulthood (Sacker, Schoon, & Bartley, 2002; Deary et al., 2005). This could potentially explain why the risk of being overweight or obese is also increased in those from low socioeconomic status groups (Ball & Crawford, 2005; Sobal & Stunkard, 1989; Vernay et al., 2009). The Scottish Health Survey of 2008 reported that men and women in the most deprived areas had the highest age-standardized prevalence of obesity (Gray & Leyland, 2009).

We hypothesized that the apparent obesity/overweight-related risk of impaired cognition in adulthood, and possibly old age, is principally a result of a lower previous ability and socioeconomic status. It is also possible that poor health status may confound the relationship between BMI and cognition. Those who are less healthy are more likely to become cognitively impaired. Examining the possibility of reverse causation (where the effect has preceded the cause)—that is, that early life IQ is an antecedent of

both BMI and old-age cognition—requires a sample of individuals for whom there is a measure of intelligence from their early life, but this is rarely available. The Lothian Birth Cohort 1936 Study (LBC1936) is advantageous for examining the effects of BMI and cognitive function in later life for several reasons: The cohort is unusual in having validated measures of cognitive ability from ages 11 and 70 years; the availability of possible confounding health and demographic information; and a large cognitive test battery at age 70. The cross-sectional aspect of the design of the present study was such that we could investigate the relationship between BMI and cognitive ability in old age. There was also a longitudinal aspect: By controlling for childhood IQ, we could additionally examine the relationship between cognitive change across the lifespan and later BMI. We emphasize that this was not a fully longitudinal investigation, given that BMI is only measured at one time point (old age). The specific aims of the present study were to investigate whether a higher BMI in later life is associated with poorer cognitive outcomes and whether these relationships are substantially accounted for (confounded) by previous cognitive ability (age 11 IQ), socioeconomic status, and/or health measures. Cognitive assessment at age 70 included multiple markers of general cognitive ability, memory, speed of information processing, and verbal ability.

Method

Participants and General Method

We analyzed data collected from the LBC1936, which comprises 1,091 men and women aged ~70 years at the first time of testing in old age. These individuals are surviving participants of the Scottish Mental Survey of 1947 (SMS1947; see Deary, Whalley, & Starr, 2009). The SMS1947 tested the mental ability of almost all Scottish schoolchildren born in 1936 and attending school on June 4th, 1947 (mean age, 11 years), with a well-validated test of general intelligence: a version of the Moray House Test No. 12 (MHT; Scottish Council for Research in Education [SCRE], 1933, 1949). Full details of the recruitment and testing of the LBC1936 are given in a free-access protocol paper (Deary et al., 2007). At the time of recruitment, LBC1936 members mostly resided in Edinburgh and its surrounding area (Lothian) in Scotland. They were relatively healthy and lived independently. Between 2004 and 2007, LBC1936 participants attended the Wellcome Trust Clinical Research Facility at the Western General Hospital in Edinburgh to undergo cognitive testing, a clinical assessment, and an interview and to take home a large questionnaire to be completed and posted back. Cognitive testing was conducted by trained researchers and the physical assessments by research nurses. The structured interview ascertained demographic information and medical history. As a part of their general assessment, LBC1936 participants completed a set of diet, personality, and lifestyle questionnaires (Deary et al., 2007). Of the 1,091 participants interviewed, 1,090 had height and weight measurements taken, enabling BMI to be calculated. Eleven individuals were identified as having potential dementia, on the basis of a score of <24 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and were excluded from the analyses. The final sample for analysis in the present study comprised 1,079 people (for age, $M = 69.5$ years, $SD = 0.8$ years) at

the time of testing. Ethics permission for the LBC1936 protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee (LREC/2003/2/29). The research was conducted in compliance with the Helsinki Declaration. All participants gave their written, informed consent.

Procedure

Measurement of BMI. Trained research nurses measured height and weight as part of a physical examination using a standardized protocol. Height (in centimeters) was measured with a SECA stadiometer on individuals not wearing shoes. The research nurses measured weight (in kilograms) for individuals without outer clothing or shoes using electronic SECA scales with a digital readout. BMI was calculated as weight (in kilograms) divided by height squared (in square meters).

Measurement of cognitive performance at age 70. A full description of the cognitive tests and administration procedures can be found in the free-access LBC1936 protocol article (Deary et al., 2007). Brief descriptions of the tests follow.

The MMSE is a test of global cognitive function (Folstein et al., 1975) and commonly used by clinicians and researchers as a screening test for cognitive impairment. Scores range from 0 to 30, with a score of less than 24 often used to indicate possible dementia.

From the Wechsler Adult Intelligence Scale—III^{UK} (WAIS—III; Wechsler, 1998a) we included Digit Symbol Coding (for speed of information processing), Block Design (for constructional ability), Matrix Reasoning (for nonverbal reasoning), Digit Span Backwards (for working memory), Symbol Search (for speed of information processing), and Letter–Number Sequencing (for working memory).

From the Wechsler Memory Scale—III^{UK} (WMS—III; Wechsler, 1998b) we used Logical Memory I and II (for verbal declarative memory and for immediate and delayed recall), Verbal Paired Associates I and II (for verbal learning and memory and for immediate and delayed recall), and Spatial Span (for nonverbal spatial learning and memory).

The National Adult Reading Test (NART; Nelson & Willison, 1991) and Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) are widely used to estimate previous cognitive ability, and they require the pronunciation of irregular words. Simple and Four-Choice reaction time (RT) tasks measure speed and variability of simple information processing with a purpose-built portable box (Cox, Huppert, & Whichelow, 1993; Deary, Der, & Ford, 2001). Inspection Time is a computer-based task used to assess speed of elementary visual processing with no requirement for speeded reactions (Deary, Simonotto, et al., 2004).

The MHT (SCRE, 1933, 1949), previously taken by participants in the SMS1947 at age 11, was repeated at their clinic visit aged about 70. The MHT comprises 71 items (mostly verbal reasoning, but also some numerical, spatial, and other items) and has a maximum possible score of 76 and a 45-min time limit. MHT scores were corrected for age in days at time of testing and converted to an IQ scale where $M = 100$ and $SD = 15$.

Covariates, including childhood IQ. Data on age, education (number of years full time), marital status (married, widowed, unmarried/divorced), smoking status (current, ex-smoker, or never

smoked), and alcohol intake (units per week) were collected by structured interview. A medical history was taken including diagnoses of hypertension, diabetes, CVD, high cholesterol, and stroke (such diseases are associated with obesity). A physical activity measure (days per month of exercise) was obtained from a self-report questionnaire booklet comprising various social and life-style questions. Childhood (age 11) MHT scores were obtained, in collaboration with SCRE and with the permission of LBC1936 participants, from the original SMS1947 records. This mental test was concurrently validated against the Terman–Merill revision of the Binet scales (SCRE, 1949). The test conducted at age 11 reflects cognitive functioning toward the end of primary school education and is a valid measure of early life ability. As before, age 11 MHT scores were corrected for age in days at time of testing and converted to an IQ scale where $M = 100$ and $SD = 15$. In this sample, the correlation between age 11 and age 70 MHT-derived IQ is .69 ($p < .001$). Social class was derived from participants' highest reported occupation and consisted of 6 categories: I (professional occupations); II (managerial and technical occupations); and III (skilled occupations)—divided into IIIN (nonmanual) and IIIM (manual)—IV (partly skilled occupations); and V (unskilled occupations; Office of Population Censuses and Surveys, 1980). Because of the small number of participants in class V, classes IV and V were combined. The women in the cohort were asked for their husband's occupation as well as their own and were assigned a social class based on the highest occupation of the household. This was derived from their own occupation for about half of the women and from the husband's occupation for the remainder.

Statistical Analyses

For descriptive purposes, participants were categorized according to standard BMI classification by the World Health Organization (WHO, 2000); namely, underweight (<18.5), normal weight (18.5 – 24.99), overweight (25 – 29.99), or obese (≥ 30). We used analysis of variance and chi-square tests to examine whether demographic and health variables differed between BMI categories. The main analyses examined the associations between BMI (as a continuous variable) and cognitive function outcome scores at age 70 using general linear models (GLMs). Seven models were fitted to the data, each including adjustment for potential confounding factors. Although there was a relatively small difference in age across this birth cohort, assessment took place over a period of 3 years, and age (in years) at assessment ranged from 67.7 to 71.3. Therefore, we adjusted for the effects of chronological age in each model. Both age (in days at time of testing) and gender were included as covariates in all models. The second model included occupational social class. The third model included age 11 IQ to control for early life cognitive ability, and the fourth model included education. The fifth and sixth models included health behaviors and health measures, respectively. The final and seventh model included all the covariates mentioned.

A general cognitive ability component score (g factor) was derived from principal-components analysis (PCA) of six WAIS—III subtests (Letter–Number Sequencing, Matrix Reasoning, Block Design, Digit Symbol, Digit Span Backwards, and Symbol Search). A general processing speed component score (speed) was similarly derived from a PCA of the set of speed measures (Sym-

bol Search, Digit Symbol, Simple RT mean, Four-Choice RT mean, and Inspection Time). The extraction of these factors by PCA has been described elsewhere (Luciano et al., 2009). Using the same method, we extracted a general memory factor (memory) from the WMS-III subtests (Logical Memory I Immediate and II Delayed Recall, Spatial Span Forwards, Spatial Span Backwards, Verbal Paired Associates I Immediate and II Delayed Recall) and two WAIS-III subtests (Letter-Number Sequencing and Digit Span Backwards). The first unrotated principal components for the *g* factor, processing speed factor, and memory factor, explained 53%, 51%, and 43% of the variance, respectively. The fourth cognitive outcome variable used in the present study is age 70 MHT-derived IQ. Additional analyses were performed with NART and WTAR scores. We present relevant estimates of effect size (η_p^2) in addition to *p* values.

Results

Descriptive Characteristics

Of the 1,079 participants, 538 were men and 541 were women. The mean age was 69.5 (*SD* = 0.8). The mean BMI for the study population was 27.8, (*SD* = 4.4; range = 16.0–48.5).

Characteristics of BMI categories. Table 1 shows the main characteristics of participants according to BMI category. Of the sample, 0.6% were underweight (*n* = 7), 25.3% were normal weight (*n* = 273), 47.3% were overweight (*n* = 510), and 26.8% were obese (*n* = 290). According to criteria from the WHO (2000), nearly three quarters of the sample were either overweight or obese. As the underweight category comprised only 0.6% of the sample, we were unable to draw reliable conclusions with regard to the general characteristics of this category. With increasing BMI (in the normal weight, overweight, and obese categories), participants were significantly more likely to be male, have a more manual occupational social class, less education, a lower MMSE score, and more likely to be an ex-smoker. In terms of health measures, a higher BMI category was associated with an increased incidence of hypertension, diabetes, and CVD but not stroke or elevated cholesterol.

BMI category and cognitive outcomes at ages 11 and 70. Those with a higher BMI at age 70 were significantly more likely to have a lower childhood IQ (*p* = .03; see Table 2; the difference between being obese and being of normal weight was associated with a childhood IQ difference of 4.8 points (Cohen's *d* = .33). The higher BMI-lower IQ relationship was still apparent almost

Table 1
Characteristics of the Study Population by BMI Category (Mean Values and % Prevalence)

Sociodemographic variable	Total sample (<i>N</i> = 1,079)		Underweight (<i>n</i> = 7)		Normal weight (<i>n</i> = 273)		Overweight (<i>n</i> = 510)		Obese (<i>n</i> = 289)		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Age (years)	69.5	0.83	69.3	0.8	69.5	0.9	69.5	0.8	69.6	0.8	.07
Gender											<.001
% Male (<i>n</i> = 538)	49.9		0		39.9		55.1		51.2		
% Female (<i>n</i> = 541)	50.1		100		60.1		44.9		48.8		
Marital status											.71
% Married	71.2		57.1		70.0		73.7		68.2		
% Widowed	13.5		28.6		12.4		12.3		16.3		
% Unmarried/divorced	15.3		14.3		17.6		14.0		15.5		
Social class											.002
I	17.9		28.6		20.0		17.8		15.7		
II	37.6		42.9		39.6		40.0		31.3		
IIIN	23.2		28.6		28.1		20.4		23.5		
IIIM	17.4		0		9.3		18.2		24.2		
IV + V	3.9		0		3.0		3.6		5.3		
Education (years full time)	10.7	1.1	10.6	0.8	10.9	1.2	10.7	1.1	10.6	1.1	.01
MMSE	28.9	1.3	29.3	1.1	29.1	1.2	28.8	1.3	28.8	1.3	.02
Health behaviors											
Alcohol intake (units/week)	10.5	14.2	3.4	4.3	10.8	14.2	10.6	13.3	10.3	15.8	.59
Physical activity (days/month)	7.6	8.1	5.1	10.5	8.4	8.5	7.5	7.8	7.2	8.1	.30
Smoking status											<.001
% Nonsmokers	43.6		28.6		46.9		43.5		41.2		
% Ex-smokers	43.2		28.6		33.3		43.9		51.5		
% Current smokers	13.2		42.8		19.8		12.5		7.3		
Health measures											
% With hypertension	39.6		28.6		24.5		39.2		54.7		<.001
% With diabetes	8.2		0		2.2		8.0		14.2		<.001
% With CVD	24.6		28.6		19.4		22.3		33.2		.001
% With cholesterol	35.3		14.3		32.7		35.5		38.1		.37
% With stroke	5.0		0		4.0		5.9		4.1		.53

Note. Social classes are categorized as follows: I (professional occupations); II (managerial and technical occupations); and III (skilled occupations)—divided into IIIN (nonmanual) and IIIM (manual)—IV (partly skilled occupations); and V (unskilled occupations). *p* values are from *t* tests, analyses of variance, and chi-square tests as appropriate. BMI = body mass index; MMSE = Mini-Mental State Examination; CVD = cardiovascular disease. Probabilities for significant effects are given in boldface.

Table 2
Cognitive Outcomes by BMI Category, With Reported Means and *p* Values

Variable	<i>M</i> (and <i>SD</i>) for:				<i>p</i>
	Underweight (<i>n</i> = 7)	Normal weight (<i>n</i> = 272)	Overweight (<i>n</i> = 510)	Obese (<i>n</i> = 290)	
Age 11 IQ ^a	102.3 (14.2)	102.7 (14.7)	100.0 (14.9)	97.9 (14.7)	.003
Age 70 IQ ^a	93.2 (20.1)	102.2 (13.3)	100.2 (14.1)	99.2 (14.7)	.037
<i>g</i> Factor ^b	−0.26 (0.92)	0.12 (0.92)	0.04 (1.03)	−0.11 (0.93)	.025
Processing speed ^b	−0.37 (0.64)	0.10 (0.94)	0.05 (1.02)	−0.09 (0.94)	.091
Memory ^b	−0.18 (1.7)	0.05 (0.99)	0.02 (0.98)	−0.02 (0.95)	.799
NART	37.4 (12.0)	36.4 (7.6)	34.4 (8.1)	33.1 (8.0)	<.001
WTAR	43.4 (10.2)	42.9 (6.1)	40.9 (7.2)	39.8 (7.2)	<.001

Note. BMI = body mass index; NART = National Adult Reading Test; WTAR = Wechsler Test of Adult Reading.

^a Age 11 and age 70 Moray House Test No. 12 scores were corrected for age (in days at time of testing) and converted to standard IQ-type scores where *M* = 100 and *SD* = 15. ^b Cognitive-component scores derived from principal-component analysis. These are standard scores, with *M* = 0 and *SD* = 1 in the whole sample. Probabilities for significant effects are given in boldface.

60 years later. At age ~70, participants in the obese category scored on average 3 points less (Cohen's *d* = .22) on the same measure of IQ (as that taken at age 11) than those in the normal weight BMI category. A similar relationship was seen across the cognitive domains representing general ability (*g* factor) and verbal ability (NART and WTAR), whereby overweight and obese participants scored significantly more poorly than those of normal weight. Performance on processing speed and memory tasks did not differ significantly between BMI categories, although a similar inverse trend was observed. Although the mean childhood IQ score of the underweight group exceeded those of the overweight and obese groups, by age 70 they performed significantly worse on tests of general cognitive ability, processing speed, and memory but higher than all of their counterparts on the verbal ability tests. However, these results should be interpreted with caution, given the small size of the group and the large standard errors for their cognitive test scores at age 70.

General Linear Models

Seven GLMs were fitted to the data for examination of the contribution of BMI (as a continuous variable) and potentially confounding variables to cognitive function at age 70 (see Table 3). In the initial age- and gender-adjusted model, BMI was significantly, inversely associated with performance on tests of age 70 IQ, general cognitive ability (*g* factor), the NART, and the WTAR; the largest effect sizes were seen for the NART and WTAR. The BMI–processing speed association narrowly missed conventional significance, at *p* = .051. When occupational social class (Model 2), age 11 IQ (Model 3), and education (Model 4) were independently added to the base model, those previously significant associations with age 70 IQ and the *g* factor almost all became nonsignificant (the relationship between BMI and *g* factor in Model 4 remains marginally significant at *p* = .045), and their effect sizes were markedly attenuated; in the case of age 11 IQ, totally attenuated. Model 5, which has age, gender, and health

Table 3
Associations Between BMI Score and Cognitive Outcomes at Age 70 (General Linear Models, *p* Values and Associated Partial Eta-Squared Values)

Model	Age 70 IQ (<i>n</i> = 1,069) ^a		<i>g</i> factor (<i>n</i> = 1,062)		Processing speed (<i>n</i> = 1,028)		Memory (<i>n</i> = 1,037)		NART (<i>n</i> = 1,077)		WTAR (<i>n</i> = 1,077)	
	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2
1. Gender + age	.002	.009	.001	.010	.051	.004	.13	.002	<.001	.028	<.001	.033
2. Gender + age + social class	.26	.001	.18	.002	.85	.000	.76	.000	<.001	.013	<.001	.017
3. Gender + age + age 11 IQ	.92	.000	.69	.000	.72	.000	.11	.003	.003	.009	<.001	.014
4. Gender + age + education	.082	.003	.045	.004	.36	.001	.76	.000	<.001	.016	<.001	.021
5. Gender + age + health behaviors	.010	.007	<.001	.013	.038	.005	.059	.004	<.001	.038	<.001	.039
6. Gender + age + health measures	.015	.006	.040	.004	.36	.001	.33	.001	<.001	.021	<.001	.025
7. All covariates	.42	.001	.31	.001	.18	.002	.31	.001	.025	.006	.011	.008

Note. *p* values in bold represent significant negative associations between BMI score and cognitive outcome. Health behaviors = alcohol consumption, smoking, and physical activity; health measures = CVD, hypertension, and diabetes.

^a Age 70 IQ is already age adjusted (age is not included in the models for this outcome variable).

behaviors as covariates, showed significant effects of BMI on age 70 IQ, the *g* factor, and processing speed, with effects sizes almost as large, or larger, than the baseline model with just age and gender as covariates. The BMI–NART and BMI–WTAR inverse associations remained significant throughout each of the models, although their effects sizes were reduced by about 50%. BMI associations with these two outcomes also remained significant in those models controlling for health behaviors (Model 5), health measures (Model 6), and the final (all-inclusive) Model 7. By Model 7, which includes all covariates, there was some greater attenuation, but the associations remained highly significant (for the NART, $p = .025$; for the WTAR, $p = .011$). Finally, we ran the models with interaction terms—BMI \times Age 11 IQ, BMI \times Social Class, and BMI \times Health (with history of CVD as a marker of health)—to investigate whether there were any modifying effects of age 11 IQ, social class, or health. We found no modifying effect of social class or health and a small moderating effect of age 11 IQ on the relationship between BMI and age 70 IQ only. However, this result was only marginally significant, and the effect size was minimal ($p = .049$, $\eta_p^2 = .004$).

Discussion

This study had several main findings. First, about three quarters of our sample of 70-year-old participants were found to be either overweight or obese, according to standard WHO criteria (WHO, 2000). Second, unadjusted associations showed a link between higher old-age BMI (indicative of overweight or obesity) and poorer cognitive performance at age 70 on tests of IQ, general cognitive ability, and verbal ability but not processing speed or memory. These results were consistent with previous reports (e.g., Cournot et al., 2006; Dahl et al., 2009) showing an inverse relationship between BMI in midlife and later life cognition. The third and most novel finding in this study is that current cognitive performance was not associated with BMI after adjusting for previous ability and occupational social class. However, there was one exception: A higher BMI was related to poorer verbal ability (crystallized intelligence) regardless of age 11 IQ, social class, health behaviors, and health measures.

Cognitive abilities in old age are most strongly predicted by one's previous cognitive ability; previous research derived from longitudinal studies of large birth cohorts reveal that childhood IQ accounts for the majority of variance in adult IQ. IQ is relatively stable across the lifespan, regardless of many other factors (Deary et al., 2000; Deary, Whiteman, Starr, Whalley, & Fox, 2004). In the present sample, those with a high early life IQ were much more likely to have a high later life IQ. Variation in people's cognitive ability at age 70 is made up of variation in the lifelong (stable) trait of intelligence, variation in any lifetime relative change in intelligence among the cohort, and some amount of measurement error (which is unavoidable). Having a measure of childhood IQ enabled an estimation of how "bright" an older person is in relation to how "bright" he or she was, plus or minus any change relative to peers in the cohort over the life course. Examining the cross-sectional data (i.e., the relation between the BMI and cognitive abilities measured at the endpoint [old age]) at first appeared to suggest that those who were overweight or obese in later life were more likely to show age-related cognitive disadvantage. However, the present study differs from others in that, by controlling for age 11 IQ, we

were able to show that it is the relationship between old-age BMI and the lifetime stable trait of intelligence that is of prime importance.

In the present study, we found strong evidence of an association between early life IQ and age 70 BMI. This finding is consistent with the growing number of studies linking childhood IQ with later adiposity, disease, and mortality (Chandola et al., 2006) and many aspects of both diet and health-related lifestyle (e.g., physical activity) in large population representative samples (Batty et al., 2007; Chandola et al., 2006). The risk of overweight or obesity also varied across social class groups, as previously reported by others (Vernay et al., 2009). Those belonging to the manual social class groups (IIIM, IV, and V) tended toward a higher BMI. People with a lower premorbid intelligence are generally more socioeconomically disadvantaged. However, because a childhood IQ measure precedes any effects of later health, lifestyle, or socioeconomic circumstances, it is plausible that there is a chain of influence on BMI, beginning with childhood cognitive ability, which is then mediated by socioeconomic circumstances through educational and occupational attainment (Johnson, Brett, & Deary, 2010) and lifestyle factors (including diet and health management). We suggest that our findings provide evidence indicative of reverse causation, whereby the effect (lower cognitive ability) actually precedes the assumed cause (higher BMI). Alternatively, there may be a previous common cause to both cognitive ability and overweight, given that there is some evidence to suggest that the IQ–BMI relationship may be present even in very early childhood. Guxens et al. (2009) found that preschool children with a higher cognitive ability at age 4 had a lower BMI at age 6. Childhood IQ may be an intrinsic indicator of general "bodily integrity" (Whalley & Deary, 2001). Given that food choices in young children are governed chiefly by their parents (compared with being self-feeding adults), it is possible that the underlying mechanism in this relationship is environmental circumstances, including parental IQ. In the context of the present study, these results suggest that, rather than adult health behaviors being the mediating factor between IQ and BMI, we must also consider that there may be common underlying etiologies present in early life that lead to both obesity and poorer neurodevelopment. This may warrant future investigation.

If previous ability accounts for most of the association between BMI and cognition in old age, then why do we find a decrement in verbal ability in the overweight and obese, even after adjusting for age 11 IQ, socioeconomic status, health behaviors, and health measures? Whereas performance in other cognitive domains tends to decline with age, verbal ability is relatively immune to the effects of both aging (Carroll, 1993; Hedden & Gabrieli, 2004; McGurn et al., 2004; Schaie, 1996) and health factors. The NART and WTAR are widely believed to reflect crystallized intelligence, which, unlike fluid intelligence, remains relatively intact as people age. Performance is thought to reflect peak adult intelligence (beyond the abilities measured in standard IQ-type tests), which is related to education and intellectual, social, and cultural development across the lifespan. Peak adult ability is likely to be associated with lifestyle preferences that influence the maintenance of a healthy weight.

A higher BMI was also associated with poorer health (as expected), in terms of an increased incidence of hypertension, CVD, and diabetes. There is no doubt that being overweight has signif-

icant, adverse effects on one's physical health and quality of life. However, in this and previous studies, controlling for health indices such as CVD and diabetes had little effect on the BMI–cognition association (Dahl et al., 2009; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009). If cognition at age 70 was mediated by the physical consequences of BMI, we would expect such health measures to cause some substantial attenuation. Given the links between previous cognitive ability, morbidity, and mortality previously identified by various authors, it is plausible that variations in premorbid IQ are also partly contributing to these adverse health outcomes, again perhaps through lifestyle choices.

Our study has the following strengths. These analyses make a novel contribution to this area of research. This is, to our knowledge, the first study to examine the relationship between BMI and cognitive performance that can statistically control for a measure of premorbid IQ. Some previous studies have examined the confounding effects of education, but IQ measured in childhood is a better predictor of cognitive function in adulthood than education. Studies with early life IQ data are rare and offer a unique insight in the investigation of factors affecting cognition with aging. Our results are useful in reconsidering results of previous epidemiological investigations, which have typically focused on a direction of causation suggestive of adverse physical and mental (including cognitive) effects, as a result of excess adiposity. However, most epidemiological data do not allow a firm conclusion to be drawn about a causal relationship between body weight and cognitive abilities. Whereas there is no doubt that there is a link between overweight/obesity and both degenerative disease and cognitive impairment, our data are suggestive of reverse causation. As hypothesized, the outcomes in the present study (and other BMI–cognition investigations) were subject to multidirectional influences that are associated with variation in previous cognitive ability. That is, early life IQ influences, perhaps indirectly, the development of overweight/obesity (Gustafson, 2008), as well as adult cognitive ability.

Second, we used direct measurements of height and weight, taken at the time of testing by trained research nurses. Using standard measurement procedures and instruments rather than self-report data (on which many previous results have been based) is more likely to provide accurate BMI scores. Third, the LBC1936 used a comprehensive neuropsychological test battery, atypical for most epidemiological studies. This allowed an examination of the effects of BMI on different cognitive domains, whereas others have relied on only very crude measures of cognitive function, such as the MMSE (e.g., Ng et al., 2008; Sakakura et al., 2008).

There are some methodological limitations to consider. There were very few underweight individuals in the present study, so we were unable to explore the association between a low BMI and cognitive function. It has been reported that a very low BMI or weight loss are often preclinical markers of dementia in the elderly (Atti et al., 2008). However, a low frequency of underweights is typical of healthy populations without dementia. Although the present study lacked sufficient statistical power to detect any true associations, we noted a trend for poorer cognitive ability in the underweight category at age 70 (not present in childhood) that may warrant further investigation. A second limitation was the use of BMI in an older population. BMI is a useful, general index of a person's weight relative to their height, but it does not take into account the decreasing bone mass, muscle mass, and height asso-

ciated with aging (West & Hann, 2009). Therefore, using BMI in the elderly may lead to an overestimation of body weight. That said, we were investigating the effects of BMI within a narrow age range, so this would have a minimal effect on results. BMI does not specifically reflect abdominal fat accumulation, unlike a waist circumference measure (Harris et al., 2000). Abdominal adiposity is reported to be a more potent predictor of vascular and metabolic diseases than BMI (Dahl et al., 2009) and confers an increased risk for dementia and cognitive impairment (West & Haan, 2009; Whitmer et al., 2008). However, a recent study has found that obesity indices (including BMI and waist–hip ratio) are not differentially related to neurocognitive outcomes both cross-sectionally and longitudinally, as previously believed (Gunstad, Lhotsky, Wendell, Ferrucci, & Zander, 2010). Unfortunately, no measure of abdominal adiposity was available in this data set.

A third limitation was the lack of information regarding weight history. Weight can often decrease in old age (Johnson, Wilkins & Morris, 2006) as a result of illness, poor appetite, poor diet, and age or disease-related loss of height. BMI at age 70 may not be representative of lifetime or even midlife BMI. Given that participants in the study were generally healthy, it is unlikely that this limitation would have a significant effect on results. Aside from being generally healthy, the LBC1936 participants, as self-selecting study volunteers, are a relatively able group (in mind and body) compared with the original, national sample who participated in the SMS1947. Furthermore, Edinburgh is a relatively affluent area and scored higher, on average, than all other areas in the survey (SCRE, 1949). Because of this potential healthy survivor effect, our results may not be representative of Scotland as a whole, or even the United Kingdom. However, within our sample, we were confident that there was a wide range of cognitive abilities and individuals from all occupational social class groups. Moreover, if the range of abilities represented is slightly narrower than a random sample of the population, our findings, if anything, are more likely to underestimate any BMI–cognition associations.

Conclusion

In conclusion, the present study found that the relationship between a higher BMI and poorer cognition in later life is largely an artifact of confounding by a lower childhood IQ and occupational social class. The results suggest that a predisposition to weight gain in adult life is determined, to some extent, by early life circumstances. Although being overweight or obese was linked with a poorer verbal ability in old age (even after controlling for previous ability), we propose that this is not evidence of a direct causal effect but probably a reflection of cognitively and socially patterned subsequent adoption of healthy lifestyles in adulthood. We conclude that there is no evidence that obesity contributes directly to premature brain aging. Rather, there exists a complex relationship between IQ, social circumstances, and BMI involving multiple pathways that interact with each other. One possible mechanism is that those of higher ability maintain a healthy weight by engaging in a healthy lifestyle that protects against cognitive decline. Alternatively, there may be common underlying etiologies present in early life that lead to both obesity and poorer neurodevelopment.

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Alcohol Intake and Cognitive Abilities in Old Age: The Lothian Birth Cohort 1936 Study

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Objective: Moderate alcohol consumption has been associated with better cognitive performance in late adulthood, possibly by improving vascular health. Few studies have examined the potentially confounding roles of prior cognitive ability and social class in this relationship. **Method:** Participants were 922 healthy adults about 70 years old in the Lothian Birth Cohort 1936 study, for whom there are IQ data from age 11. Alcohol consumption was obtained by self-report questionnaire. Cognitive outcome measures included general cognitive ability, speed of information processing, memory, and verbal ability. **Results:** Moderate to substantial drinking (>2 units/day) was associated with better performance on cognitive tests than low-level drinking (≤ 2 units/day) or nondrinking in men and women. After adjusting for childhood IQ and adult social class, most of these associations were removed or substantially attenuated. After full adjustment, a small, positive association remained between overall alcohol intake and memory (women and men) and verbal ability (women only). Women's overall alcohol intake was derived almost exclusively from wine. In men, effects differed according to beverage type: wine and sherry–port consumption was associated with better verbal ability, but beer was associated with a poorer verbal ability and spirits intake was associated with better memory. **Conclusions:** Prior intelligence and socioeconomic status influence both amount and type of alcohol intake and may partly explain the link between alcohol intake and improved cognitive performance at age 70. Alcohol consumption was found to make a small, independent contribution to memory performance and verbal ability, but these findings' clinical significance is uncertain.

Keywords: alcohol, cognitive function, childhood IQ, aging

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Moderate alcohol intake in middle-aged and older adults is associated with reduced all-cause mortality and a lower risk of cardiovascular disease (Naimi et al., 2005). Population-based studies have found that moderate drinking, compared with abstinence, can also benefit cognitive function (Espeland et al., 2005; Lang, Wallace, Huppert, & Melzer, 2007; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005). Evidence from longitudinal assessments of older people has suggested that light to moderate drinking has a

protective effect against cognitive decline over time (Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005; Wright, Elkind, Luo, Paik, & Sacco, 2006). Stampfer et al. (2005) reported that those who drank up to 15 mg of alcohol per day (not more than about one drink) had a 20% decreased risk of cognitive impairment at baseline, compared with nondrinkers, and these moderate drinkers experienced less cognitive decline over a 2-year period. Some studies have reported a positive association between moderate

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alcohol intake and improved cognitive performance in women, but not in men (Dufouil, Ducimetière, & Alperovitch, 1997; Leroi, Sheppard, & Lyketsos, 2002; McGuire, Ajani, & Ford, 2007; Stott et al., 2008), and others have reported a significant effect in both sexes but a larger effect size in women (Britton, Singh-Manoux, & Marmot, 2004). A few studies have failed to find any positive cognitive benefit of nonexcessive alcohol consumption (Cervilla, Prince, & Mann, 2000; Elwood et al., 1999). Inconsistencies may be attributable to methodological issues; a meta-analysis found that definitions of moderate drinking vary widely across studies (Peters, Peters, Warner, Beckett, & Bulpitt, 2008).

The "beneficial" cognitive effects of moderate alcohol intake are reportedly heterogeneous, concentrated in areas of learning, executive functions, and psychomotor speed (Ganguli et al., 2005); verbal knowledge and phonemic fluency (Britton et al., 2004); and in a women-only study, verbal knowledge, phonemic fluency, and fine motor speed (Espeland et al., 2006). These, and many other studies, have not found strong evidence of an association between alcohol intake and memory. At present, how different types of alcoholic beverage are associated with cognitive function in late life is unclear. Few epidemiological studies have looked further than overall alcohol intake. There is some suggestion that wine, but not spirits or beer, is protective against cognitive decline (Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004) and dementia (Truelsen, Thudium, & Grønbaek, 2002). The proposed explanation is based on the antioxidant activity of the flavonoids found in wine. However, not all studies have reported consistent results. According to the Nurses' Health Study, using data derived from 12,480 older women, no significant differences in risk of cognitive impairment or decline were observed according to type of alcoholic beverage (Stampfer et al., 2005).

Typically, the direction of causation that is studied and assumed is from alcohol to cognitive ability, especially in old age. The most widely accepted mechanism behind the putatively protective role of alcohol on cognitive aging is an indirect benefit via a reduced risk of vascular disease. A quantitative review of moderate alcohol intake and biological markers of coronary heart disease risk reported a causal association via alcohol-induced changes in lipids and hemostatic factors (Rimm, Williams, Fosher, Criqui, & Stampfer, 1999). Further support for an effect on brain vasculature comes from MRI studies that have revealed a lower prevalence of white matter abnormalities and infarcts in older people with moderate alcohol intake than in nondrinkers (Mukamal, Longstreth, Mittleman, Crum, & Siscovick, 2001). However, it is also possible that the observed relation between alcohol and cognitive health is attributable to prior intelligence. Previous studies have reported that intelligence influences the amount and type of alcohol intake. People with a higher IQ tend to drink regularly but moderately (British Medical Association, 2008). Higher IQ scores have also been associated with a preference for wine over other types of alcohol in later life (Mortensen, Sørensen, & Grønbaek, 2005). If moderate drinkers are, on average, more intelligent than nondrinkers, the reported beneficial effect of moderate drinking on cognitive function in adulthood may be confounded by prior ability. Similarly, drinking appears to have social gradients. In the Whitehall study, some of the association between alcohol consumption and cognitive function could be explained by social position, as measured by employment grade (Britton et al., 2004). Variations in both IQ and socioeconomic status (SES) may play important

confounding roles in the alcohol–cognition relationship, yet many studies have attributed causal effects of alcohol intake to improved cognition in the absence of this kind of data.

The sample in this study is unusual in having validated measures of cognitive ability from childhood and old age and a range of sociodemographic and health data. Our objectives in this study were to examine whether (a) a pattern of light to moderate drinking is associated with better cognitive outcomes in old age than is nondrinking; (b) the effects on cognitive outcomes vary by type of alcoholic beverage; and (c) specifically, whether these relationships could be attributed to confounding by prior cognitive ability (age 11 IQ), SES, or both.

Method

Participants

Participants were enrolled on the Lothian Birth Cohort 1936 (LBC1936) study, which includes 1,091 men and women. These individuals are surviving participants of the Scottish Mental Survey of 1947 (SMS1947; see Deary, Whalley, & Starr, 2009). Full details of the recruitment and testing of the LBC1936 are given in a free-access protocol paper (Deary et al., 2007). At the time of recruitment, LBC1936 members mostly resided in Edinburgh and its surrounding area (Lothian) in Scotland. They were relatively healthy and lived independently. Between 2004 and 2007, at a mean age of about 70, LBC1936 participants attended the Wellcome Trust Clinical Research Facility in Edinburgh to undergo cognitive testing, a clinical assessment, and an interview. As a part of their general assessment, participants were asked to complete a Food Frequency Questionnaire (FFQ). Of the 1,091 participants interviewed, 922 (84.5%) provided both alcohol consumption and cognitive data and formed the present study sample. Ethics permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from the Lothian Research Ethics Committee (LREC/2003/2/29). The research was carried out in compliance with the Helsinki Declaration. All participants gave their written informed consent.

Procedure

Measurement of alcohol intake. Alcohol intake was assessed using the Scottish Collaborative Group 165-item FFQ, Version 7.0 (<http://www.foodfrequency.org>). The FFQ (Masson et al., 2003) has good repeatability (dietary intake in later life is reasonably stable in the short term) and good validity for most nutrients in community-dwelling older populations (Jia, Craig, Aucott, Milne, & McNeill, 2008; McNeill, Winter, & Jia, 2009). It is also a valid assessment tool for measuring alcohol intake; there is good agreement between the FFQ and 4-day weighed diet records in men ($r = .83$) and women ($r = .70$; Masson et al., 2003). This self-report questionnaire measures alcohol use over the previous 2- to 3-month period from nine alcoholic beverages, namely, low-alcohol lager or beer; dark beer (export, bitter, or stout); light beer (lager or continental beer); white wine; red wine; sherry, port, and so forth; spirits or liqueurs; alcopops (e.g., Bacardi Breezer); and cider. Each item on the questionnaire refers to a standard measure, for example, one half-pint (beer, lager, cider)

or one pub measure (spirits). Participants mark one of nine responses to indicate frequency of consumption: rarely or never, one to three per month, one per week, two to three per week, four to six per week, one per day, two to three per day, four to six per day, or seven or more per day.

In the event of any missing responses, a letter was sent requesting the information. Using standard FFQ protocol, incomplete questionnaires (with 10 or more missing items from a total of 165) were excluded from the analyses. Thirty-nine questionnaires were incomplete, 26 were returned blank, and 98 were not returned. A total of 928 (85%) completed FFQs were returned. One on which the amount of alcohol consumed was a clear statistical outlier was later excluded, and information collected at interview revealed a history of problem drinking. Five more individuals were excluded because they were identified as having potential dementia on the basis of a score of more than 24 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). The final sample for analysis in this study consisted of 922 relatively healthy participants (445 men, 477 women) about 70 ($M = 69.5$, $SD = 0.8$) years old at time of testing. Five of these participants each had one item of missing alcohol data. Therefore, total alcohol intake could be calculated for 917 participants. We calculated the daily alcohol intake in units derived from each beverage based on U.K. government guidelines¹ and a combined total daily alcohol measure from all nine sources.

Measurement of cognitive performance at age 70. Cognitive function was assessed using a battery of neuropsychological tests. See the free-access LBC1936 protocol article for a full description of tests (Deary et al., 2007). In this study, we used three composite cognitive scores derived from principal-components analyses (PCA) to represent three distinct cognitive domains. Regression scores were calculated for the first unrotated principal component of the tests in each domain. In each case, the scree slopes and eigenvalues suggested that a single component could be extracted.

***g* Factor (general cognitive ability).** A *g* factor score, representing general cognitive ability, was derived from a PCA of scores on six Wechsler Adult Intelligence Scale—III^{U.K.} (WAIS—III; Wechsler, 1998a) subtests, namely, Letter–Number Sequencing (working memory), Matrix Reasoning (nonverbal reasoning), Block Design (constructional ability), Digit Symbol (speed of information processing), Digit Span Backwards (working memory), and Symbol Search (speed of information processing). The first unrotated principal component explained 53% of the variance, and all subtests had high loadings.

Processing speed factor. A processing speed factor was derived from a PCA of scores on a set of speed of processing measures, namely, Symbol Search (WAIS—III), Digit Symbol (WAIS—III), inspection time (computer-based task used to assess speed of elementary visual processing with no requirement for speeded reactions; Deary, Simonotto, et al., 2004), and simple (SRT) and choice reaction time (CRT; speed and variability of simple information processing; Cox, Huppert & Whichelow, 1993; Deary, Der, & Ford, 2001). The reaction time tasks were administered using a purpose-built portable machine with five response keys (1, 2, 0, 3, 4). In SRT, the participant pressed the 0 key as quickly as possible after each 0 was shown on the LED screen (20 trials). In CRT (four-choice), the participant pressed the appropriate key (1, 2, 3, or 4) according to the number that appeared on the

LED screen, as quickly as possible (40 trials). Mean SRT and CRT response time and standard deviation were calculated. The first unrotated principal component for the speed factor explained 51% of the variance, and all tests had high loadings.

Memory factor. A memory factor was derived from a PCA of scores on a set of memory measures from the Wechsler Memory Scale—III^{U.K.} (WMS—III; Wechsler, 1998b), namely, Logical Memory I Immediate and II Delayed Recall (verbal declarative memory), Spatial Span Forwards and Spatial Span Backwards (nonverbal spatial learning and memory), and Verbal Paired Associates I Immediate Recall and II Delayed Recall (verbal learning and memory; immediate and delayed recall). The first unrotated principal component explained 43% of the variance, and all tests had high loadings.

Verbal ability. Verbal ability was assessed using the National Adult Reading Test (NART; Nelson & Willison, 1991) and the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001). These tests are widely used to estimate prior cognitive ability, and each requires the pronunciation of a list of 50 irregular words.

Mini-Mental State Examination (MMSE). The MMSE is a standardized brief screening measure for cognitive pathology (Folstein et al., 1975). Scores range from 0 to 30, with a score of less than 24 often used to indicate possible dementia.

Moray House Test (MHT). Participants had previously taken part in the nationwide SMS1947 at age 11. All schoolchildren born in 1936 and attending Scottish schools on June 4, 1947, took a version of the MHT Number 12 (Scottish Council for Research in Education [SCRE], 1933, 1949), a group-administered mental test consisting of 71 items and with a time limit of 45 min. Often referred to as a verbal reasoning test, it contains items including word classification, arithmetic, spatial items, cypher decoding, same–opposites, reasoning, proverbs, practical items, analogies, and following directions. The MHT was concurrently validated against the Terman–Merrill Revision of the Binet Scales (Terman & Merrill, 1937) after the SMS1947. The correlation for both boys and girls was .81 (SCRE, 1949). The test conducted at age 11 reflects cognitive functioning toward the end of primary school education and is a valid measure of early life ability. LBC1936 participants repeated the same test about 60 years later, at about age 70, as part of the cognitive assessment. MHT scores at age 11 and age 70 were corrected for age in days at time of testing and converted to an IQ scale for which $M = 100$ and $SD = 15$. In this sample, the correlation between age 11 and age 70 IQ was .67 ($p < .001$).

Demographic and control variables. Marital status, education (years of full-time education), and smoking status (current, ex-, or never smoker) were ascertained during interview. A medical history was taken (including diagnoses of diabetes, high blood pressure, high cholesterol, cardiovascular disease, and stroke). Body mass index (BMI) was calculated from height and weight measurements taken during the physical examination. A physical

¹ Alcohol unit calculations were based on U.K. Government guidelines (http://www.direct.gov.uk/en/HealthandWellbeing/DG_10036434) as follows: half pint of lager or beer = 1 unit; half pint of low alcohol lager or beer = 0.5 units; standard glass of wine = 2 units; half pint/one bottle of cider = 1 unit; standard glass of sherry or port = 1 unit; one pub measure of spirits or liqueurs = 1 unit; one bottle of alcopops = 1.5 units.

activity measure (number of days per month of exercise) was obtained from a self-report questionnaire booklet made up of various social and lifestyle questions. Adult social class was derived from participants' highest reported occupation and consisted of six classes ranging from I (professional occupations) to V (unskilled occupations), with III (skilled occupations) divided into IIIN (nonmanual) and IIIM (manual; Office of Population Censuses & Surveys, 1980). Women were assigned a social class on the basis of the highest occupation of the household. Because of the small number of participants in Class V, we combined Classes IV and V.

Statistical Analyses

Analyses were performed using SPSS Version 14.0 (SPSS Inc., Chicago, IL). Participants were categorized as nondrinkers, low-level drinkers (≤ 2 units per day), or moderate to substantial drinkers (> 2 units per day). We used this classification to illustrate any demographic and health differences between alcohol intake groups, using analysis of variance and chi-square tests, as appropriate. The main analyses examined the associations between alcohol intake (units/day) as a continuous variable and cognitive outcome scores (separately for men and women) using general linear models. Cognitive outcomes were age 70 IQ, g factor, processing speed factor, memory factor, NART, and WTAR. Four models were fitted to the data, each including adjustment for potential confounding factors. Model 1 tested the unadjusted effects of alcohol on each outcome measure. Model 2 included age 11 IQ to control for early life ability. Model 3 included occupational social class. The final model adjusted for age 11 IQ and occupational social class in combination. We present relevant estimates of effect size, reported here as partial eta-square (η_p^2), and p values. Post hoc, we used the Sobel Test (Sobel, 1982) to test for mediating effects of occupational social class on the associations between childhood IQ and alcohol consumption. An online resource was used (<http://www.danielsoper.com/statcalc/calc31.aspx>) to calculate the Sobel Test statistic, and we report regression coefficients, standard errors, Sobel statistic (z), and p values.

Results

Descriptive

Characteristics of nonresponders. Compared with those who completed the FFQ, nonresponders ($n = 163$) were significantly more likely to be older ($p = .002$), be male ($p = .006$), belong to a less professional occupational social class, have fewer years of education, have a lower MMSE score, have lower age 11 and age 70 IQ (all $ps < .001$), and have a higher BMI ($p = .002$), and they were more likely to have had a diagnosis of diabetes ($p = .049$) or stroke ($p = .020$).

Characteristics of alcohol intake categories. The characteristics of alcohol intake categories are shown in Table 1. Fifteen percent ($n = 134$) reported no current alcohol intake (nondrinkers), 54% ($n = 497$) drank 2 units or less per day (low-level drinkers; $M = 0.8$, $SD = 0.6$), and 31% ($n = 286$) reported a daily intake of more than 2 units a day (moderate to substantial drinkers; range = 2.02–20.88, $M = 4.6$, $SD = 2.7$). There were significant gender differences between intake groups. More women than men

were non- and low-level drinkers, and more men than women were in the moderate to substantial drinking category. Nearly half the men consumed more than 2 units (equivalent to 1 pint of beer or one glass of wine) per day compared with one in six women. Apart from being male, those reporting a higher alcohol intake were significantly more likely to belong to a professional occupational social class (67% of moderate to substantial drinkers belonged to Social Class I and II, compared with 48% of the nondrinkers) and have more years of education and were less likely to be smokers. Those with a higher alcohol intake were significantly more likely to have a higher childhood IQ and a higher age 70 IQ (both $ps < .001$). Moderate to substantial drinkers had, on average, a 6.8-point higher age 11 IQ than nondrinkers and a 6.1-point higher age 70 IQ than nondrinkers. Nondrinkers were significantly more likely to have had a diagnosis of cardiovascular disease than were low or moderate to substantial drinkers. Alcohol intake was not associated with marital status, MMSE score, BMI, level of physical activity, or history of hypertension, stroke, diabetes, or high cholesterol.

Alcohol Intake Category and Cognitive Outcomes at Age 11 and Age 70

We conducted separate analyses of cognition–alcohol intake associations for men and women (see Table 2). Mean cognitive scores differed significantly between alcohol intake categories for all cognitive outcome variables in men and also in women, with the exception of age 70 IQ scores (although the trend was in the same direction). The best cognitive scores for men and women were among those drinking more than two units per day; these moderate to substantial drinkers did better on tests at age 11 and age 70 than both low-level and nondrinkers. The lowest cognitive scores were associated, almost entirely, with the nondrinkers. In an additional analysis, we reclassified drinkers into those drinking within current U.K. guidelines: 21 units per week for men ($n = 270$); 14 units per week for women ($n = 303$) and those exceeding this weekly upper limit (men, $n = 132$; women, $n = 78$). This did not appreciably change any of the associations seen in Table 2; the best cognitive scores were still found among those in the highest consumption category. These results are available from us on request.

Type of Alcohol and Associations With Childhood IQ and Social Class

Table 3 presents mean intake of each type of alcohol for men and women. The women in our sample were found to derive most of their alcohol units (80%) from wine, whereas men consumed alcohol from a larger range of sources. The mean daily alcohol intake of men (2.63 units) was more than double that of women (1.14 units; $p < .001$). Compared with women, men consumed significantly more wine, spirits, and beer. Consumption of low-alcohol beer, alcopops, and cider were very low in this older cohort; therefore, we present no further analyses using these alcohol types. We examined the relationship between alcohol intake, age 11 IQ, and social class. Intake of red wine, white wine, sherry or port, and total alcohol intake were associated with a higher childhood IQ and more professional social class ($p < .001$).

Table 1

*Characteristics of the Population by Alcohol Intake Category, With Reported Mean and *p* Values*

Sociodemographic variable	Total sample (<i>n</i> = 917) ^a		Nondrinkers (<i>n</i> = 134)		Low-level drinkers (<i>n</i> = 497)		Moderate to substantial drinkers (<i>n</i> = 286)		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Alcohol intake (units/day)	1.9	2.4			0.8	0.6	4.6	2.7	n/a
Age (in years)	69.5	0.8	69.6	0.9	69.5	0.8	69.4	0.9	.002
Sex (%)									<.001
Male	48.3		29.9		39.0		72.7		
Female	51.7		70.1		61.0		27.3		
Marital status (%)									.062
Married	72.7		64.2		71.8		78.3		
Widowed	13.2		15.0		15.1		9.1		
Unmarried/divorced	14.1		21.0		13.1		12.6		
Social class (%)									.001
I	18.9		12.4		17.3		25.1		
II	38.4		35.6		36.9		41.9		
IIIN	23.6		29.5		27.1		14.7		
IIIM	15.9		17.0		16.1		15.1		
IV + V	3.3		5.4		2.6		3.3		
Education (years full time)	10.8	1.1	10.5	0.9	10.7	1.1	11.0	1.2	<.001
MMSE	28.9	1.2	28.9	1.3	28.9	1.3	29.0	1.2	.712
Age 11 IQ	101.4	14.0	97.6	14.8	100.6	14.1	104.4	13.0	<.001
Age 70 IQ	101.7	13.2	99.0	13.3	100.4	14.2	105.1	10.3	<.001
Body mass index (kg/m ²)	27.6	4.3	27.7	4.7	27.6	4.3	27.7	4.1	.926
Physical activity (days/month)	7.6	8.1	6.9	8.6	8.0	8.4	7.3	7.1	.286
Smoking status (%)									<.001
Nonsmokers	44.4		45.5		49.5		35.0		
Ex-smokers	43.3		36.5		38.8		54.2		
Current smokers	12.3		18.0		11.7		10.8		
Hypertension, yes (%)	39.5		46.3		37.6		39.5		.193
Diabetes, yes (%)	7.5		11.9		6.4		7.3		.100
Cholesterol, yes (%)	35.1		39.5		32.4		37.8		.155
Stroke, yes (%)	4.0		6.7		3.8		3.1		.210
Cardiovascular disease, yes (%)	23.8		33.6		20.5		24.8		.006

Note. Low-level drinkers = two or fewer units/day; moderately substantial drinkers = more than two units/day; I = professional occupations; II = managerial and technical occupations; IIIN = skilled occupations, nonmanual; IIIM = skilled occupations, manual; IV = partly skilled occupations; V = unskilled occupations; MMSE = Mini-Mental State Examination; n/a = not applicable.

^a Five participants had some missing alcohol data; thus, we were unable to calculate total alcohol intake. Probabilities for significant effects are given in boldface.

General Linear Models

We fit four stages of general linear model to the data to examine the contribution of alcohol (total and by type) and potentially confounding variables to age 70 cognitive function. Table 4 presents the main general linear model results, by gender. For women, we present the effects of total alcohol intake only, because associations were found to reflect the predominant influence of wine intake on cognitive function (full results can be seen online in supplemental Table 1). Model 1 (unadjusted) showed a positive association between total alcohol (wine) intake and performance across all cognitive domains; the largest effect sizes were seen for verbal ability (NART, $\eta_p^2 = .050$; WTAR, $\eta_p^2 = .042$). When age 11 IQ and social class were added (independently) to the models, the associations with age 70 IQ, *g* factor, and processing speed became nonsignificant. The positive associations with memory and NART (but not WTAR) scores remain significant, even after controlling for age 11 IQ and social class in combination. However, effect sizes were markedly reduced. Overall, the atten-

uating effects of childhood IQ and social class on these positive associations are very substantial.

Nearly half (48%) of men's total alcohol intake came from wine, and the remainder came mainly from beer and spirits. Table 4 presents the results for total alcohol intake and wine intake (full results can be seen online in supplemental Table 2). In the initial unadjusted model, total alcohol intake was associated with significantly better test performance in all cognitive domains. The largest effect sizes were for memory ($\eta_p^2 = .035$) and age 70 IQ ($\eta_p^2 = .032$). After full adjustment, the only remaining statistical effect of overall alcohol intake on cognitive outcomes in men was a positive association with memory scores, which was also found in women. Contrary to the results found for overall alcohol intake, wine consumption in men was associated with significantly better performance on both verbal ability tests (NART, $p = .004$, $\eta_p^2 = .020$; WTAR, $p = .031$, $\eta_p^2 = .011$), and statistical significance held throughout the models. Again, we observed substantial attenuation from age 11 IQ and social class. The type of alcohol consumed by

Table 2

Alcohol Intake Category and Cognitive Outcomes for Men and Women, With Reported Mean and p Values (Analysis of Variance)

Cognitive outcome	Men				Women			
	Nondrinkers (<i>n</i> = 40; <i>M</i> [<i>SD</i>])	Low-level drinkers (<i>n</i> = 194; <i>M</i> [<i>SD</i>])	Moderate to substantial drinkers (<i>n</i> = 208; <i>M</i> [<i>SD</i>])	<i>p</i>	Nondrinkers (<i>n</i> = 94; <i>M</i> [<i>SD</i>])	Low-level drinkers (<i>n</i> = 303; <i>M</i> [<i>SD</i>])	Moderate to substantial drinkers (<i>n</i> = 78; <i>M</i> [<i>SD</i>])	<i>p</i>
Age 11 IQ	96.2 (18.3)	98.3 (15.0)	103.7 (13.1)	<.001	98.2 (13.0)	102.2 (13.3)	106.3 (12.3)	<.001
Age 70 IQ	99.8 (13.6)	100.1 (15.2)	106.0 (9.7)	<.001	98.6 (13.2)	100.7 (13.5)	102.9 (11.6)	.103
<i>g</i> factor	−0.10 (1.00)	0.02 (0.98)	0.40 (0.90)	<.001	−0.12 (0.91)	0.01 (0.92)	0.34 (0.91)	.003
Processing speed	−0.02 (0.97)	−0.03 (1.00)	0.31 (0.88)	.001	−0.22 (0.88)	0.08 (0.88)	0.34 (0.92)	<.001
Memory	−0.11 (1.00)	−0.12 (0.93)	0.24 (0.93)	<.001	−0.02 (0.94)	0.04 (0.98)	0.46 (0.88)	.002
NART	34.7 (9.2)	33.2 (7.7)	36.5 (7.5)	<.001	32.8 (7.1)	35.2 (7.7)	39.0 (6.1)	<.001
WTAR	40.9 (7.8)	40.0 (6.7)	43.2 (6.2)	<.001	40.2 (6.5)	41.5 (6.7)	44.5 (4.7)	<.001

Note. Low-level drinkers, two or fewer units/day; moderate to substantial drinkers, more than two units/day; NART = National Adult Reading Test; WTAR = Wechsler Test of Adult Reading. Probabilities for significant effects are given in boldface.

men was an important factor in relation to cognitive performance (see supplemental Table 2). Notably, wine and sherry or port consumption were associated with better cognitive performance, especially on both verbal ability tests, even after full adjustment. The converse was true of beer consumption, which was associated with poorer NART performance after adjustments ($p = .041$, $\eta_p^2 = .010$). However, spirits intake was associated with a better memory performance ($p = .004$, $\eta_p^2 = .021$).

We added interaction terms in separate models (not presented in tables) to examine whether there were any interaction effects between childhood IQ and alcohol intake, or social class and alcohol intake, on later cognitive outcomes in either sex. In women, we found no evidence of any interaction effects of childhood IQ and alcohol. However, there was a social class–alcohol interaction on age 70 IQ ($p < .001$, $\eta_p^2 = .050$) and processing speed ($p = .026$, $\eta_p^2 = .025$). Data plots suggested that the only deleterious effects of alcohol consumption on age 70 IQ and processing speed were found in the manual social classes (IIIM, IV, V). In men, we found no evidence of any interaction effects of social class on any of the cognitive outcomes. However, there was a significant Childhood IQ \times Alcohol interaction on age 70 IQ ($p < .001$, $\eta_p^2 = .044$) and significant Childhood IQ \times Wine interactions on age 70 IQ ($p < .001$, $\eta_p^2 = .043$), NART ($p < .002$, $\eta_p^2 = .023$), and WTAR ($p < .037$, $\eta_p^2 = .010$). Data plots suggested that, in those drinking less alcohol, there were stronger correlations between age 11 and age 70 IQ. That is, in those participants drinking little or no alcohol, more of the variance in their age 70 IQ scores could be accounted for by childhood ability when compared with those drinking more alcohol, among whom causes other than childhood IQ contributed more to cognitive variation in old age.

We also examined the potentially mediating effects of social class on the link between prior cognitive ability and alcohol consumption. Using the Sobel test, we identified a mediating effect of social class on both the association between childhood IQ and total alcohol consumption ($A = -.024$, $SE_A = .002$, $z = 2.99$, $p < .001$) and between childhood IQ and wine consumption ($B = -.303$, $SE_B = .098$, $z = 5.59$, $p < .001$).² The standardized beta of the direct path (age 11 IQ–total alcohol) was .020, and it was .012 after social class was introduced as a mediator. The amount of the relationship accounted for by social class was .008, represent-

ing 40% of the direct effect. For wine intake, the standardized beta of the direct path (age 11 IQ–wine drinking) was .019, and it was .008 after social class was introduced as a mediator. Therefore, the amount of the relationship between age 11 IQ and wine drinking accounted for by social class was .011, representing 58% of the direct effect.

Discussion

In this study, drinking more alcohol was associated with better cognitive performance at age 70, in comparison with low-level drinking and no drinking. Moderate to substantial drinkers had better cognitive scores across all cognitive domains tested, with the exception of age 70 IQ scores in women (although this association did not reach significance, it followed the same positive trend). In line with previous research, abstainers performed more poorly than light and moderate drinkers. However, after controlling for childhood IQ and SES, there remained little evidence of a relationship between alcohol intake and current cognitive function. Where significant effects remained, the reductions in effect sizes were striking. The apparent benefits (after controlling for IQ and SES) of a higher overall alcohol intake were confined to memory performance in both men and women. Male drinkers of wine and sherry or port also appeared to have a better verbal ability (crystallized intelligence). However, these effect sizes were modest. It is plausible that the positive alcohol–crystallized IQ associations were still significant after controlling for age 11 IQ because crystallized IQ tests measure peak ability and capture variance related to the accumulated intellectual development, and the associated lifestyle and education choices, that take place between childhood and adulthood. However, these positive effects did not extend to drinking beer. Beer intake was associated with a poorer crystallized IQ (based on NART score). Women with a higher

² A = the unstandardized regression coefficient for the relationship between social class IV and mediator; SE_A = standard error of the relationship between social class IV and mediator; B = the regression coefficient for the relationship between the mediator and the dependent variable; SE_B = the standard error of the relationship between the mediator and the dependent variable.

Table 3

Alcohol Intake by Gender and Correlations Between Alcohol (Total Sample), Age 11 IQ, and Occupational Social Class

Alcohol (units/day)	Total (<i>n</i> = 922) ^a		Men (<i>n</i> = 445)		Women (<i>n</i> = 477)		Sex differences Mann–Whitney <i>U</i> (<i>p</i>)	Age 11 IQ Spearman rho <i>r_s</i> (<i>p</i>)	Social class Spearman rho <i>r_s</i> (<i>p</i>)
	<i>M</i> (range)	% reporting	<i>M</i> (range)	% reporting	<i>M</i> (range)	% reporting			
Total alcohol	1.86 (0–20.9)		2.63 (0–20.9)		1.14 (0–15.1)		64,413.5 (<.001)	.194 (<.001)	–.158 (<.001)
Red wine	0.64	54.8	0.83	60.6	0.47	49.5	88,969.0 (<.001)	.249 (<.001)	–.291 (<.001)
White wine	0.44	56.1	0.44	51.7	0.44	60.2	98,023.5 (.034)	.169 (<.001)	–.256 (<.001)
Sherry, port, etc.	0.53	26.3	0.61	25.2	0.04	27.5	104,318.5 (.561)	.168 (<.001)	–.168 (<.001)
Spirits or liqueurs	0.42	54.7	0.69	66.3	0.16	43.8	70,256.0 (<.001)	.053 (.117)	.015 (.643)
Beer (regular and dark)	0.28	36.8	0.56	65.4	0.01	10.1	43,129.50 (<.001)	.018 (.589)	.058 (.082)

^a Total sample = 922; total sample with total alcohol units/day = 917. Probabilities for significant effects are given in boldface.

wine intake performed better on tests of crystallized IQ and memory, and those consuming spirits performed better on one of the tests of crystallized IQ (NART).

Many previous studies have concluded that alcohol consumption has a direct protective effect on cognition, via vascular mechanisms or otherwise. This study indicates that this conclusion may be erroneous. Prior ability and SES were found to significantly confound the relationship between alcohol intake and cognitive abilities in old age. These findings are in keeping with the previous literature in which higher intelligence, measured as early as childhood, was related to a higher alcohol intake in adult life (Batty et al., 2008) but fewer alcohol-induced hangovers (Batty, Deary, & Macintyre, 2006), suggestive of moderate consumption. One other study has attempted to examine the effects of prior ability on the cognitive effects of alcohol use in old age (Cooper et al., 2009). However, it used only an estimate rather than an actual measure of prior ability. Cooper et al. (2009) concluded that cognitive ability

was no longer associated with overall alcohol use once estimated premorbid IQ (NART) was controlled for. In this study, it was clear that in addition to having NART scores, it was important to have a measure of early life intelligence and also to analyze the data according to type of alcohol-based drink.

Moderate drinking has previously been reported to be more prevalent in educated, affluent classes and nondrinking more concentrated in the least educated, deprived groups (Jefferis, Manor, & Power, 2007). Our findings support those of a prior study linking alcohol intake, SES, and cognitive function, whereby a pattern of higher SES and cognitive scores was found in men consuming light to moderate levels of alcohol than in abstainers or heavy drinkers, and in female drinkers, irrespective of level consumed (Richards, Hardy, & Wadsworth, 2005).

Those with a higher IQ (even when measured in childhood) and more advantaged adult SES are more likely to develop a preference for wine and sherry or port drinking, which is consistent with

Table 4

Relationship Between Alcohol (Units/Day) and Cognitive Outcomes at Age 70, by Gender

Predictor units per day and model	Age 70 IQ (<i>n</i> = 917)		<i>g</i> factor (<i>n</i> = 898)		Processing speed (<i>n</i> = 886)		Memory (<i>n</i> = 891)		NART (<i>n</i> = 921)		WTAR (<i>n</i> = 921)	
	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2
Total alcohol												
Women												
1	.027^a	.010	.002^a	.021	.006^a	.017	<.001^a	.034	<.001^a	.050	<.001^a	.042
2	.523	.001	.156	.005	.093	.007	.024^a	.012	.006^a	.017	.007^a	.016
3	.399	.002	.054	.008	.062	.008	.002^a	.021	.000^a	.028	.003^a	.019
4	.228	.003	.123	.006	.170	.005	.043^a	.010	.048^a	.009	.084	.007
Men												
1	<.001^a	.032	.001^a	.028	.028^a	.011	<.001^a	.035	.002^a	.021	<.001^a	.030
2	.020^a	.013	.030^a	.011	.292	.003	.010^a	.016	.138	.005	.020^a	.013
3	.015^a	.014	.040^a	.010	.360	.002	.006^a	.018	.178	.004	.037^a	.010
4	.062	.009	.370	.002	.648	.001	.030^a	.012	.537	.001	.125	.006
Total wine												
Men												
1	<.001^a	.034	<.001^a	.032	.088	.007	<.001^a	.031	<.001^a	.060	<.001^a	.047
2	.035^a	.011	.022^a	.013	.771	.000	.037^a	.011	<.001^a	.042	.001^a	.028
3	.101	.006	.188	.004	.616	.001	.076	.008	.008^a	.016	.032^a	.011
4	.208	.004	.345	.002	.349	.002	.212	.004	.004^a	.020	.031^a	.011

Note. Model 1: unadjusted; Model 2: Age 11 IQ; Model 3: social class; Model 4: Age 11 IQ + social class. NART = National Adult Reading Test; WTAR = Wechsler Test of Adult Reading.

^a Denotes a positive model correlation coefficient. Probabilities for significant effects are given in boldface.

findings from other studies, suggesting that these effects are not particular to this cohort, or to Scottish culture. For example, in studies using large Danish samples, preference for wine over beer and other alcoholic beverages was linked to a higher IQ (Mortensen, Sørensen, & Grønbæk, 2005) and a higher social class (Nielsen, Schnor, Jensen, & Grønbæk, 2004; Osler, Godtfredsen & Prescott, 2008). In France, social and environmental factors have been linked to alcohol preference; wine drinking was associated with a more favorable social environment, whereas the converse was true for beer drinking (Ruidavets et al., 2004). In the United States, wine preference was associated with significantly higher level of education (Paschall & Lipton, 2005). We also found in women that the association between overall alcohol intake and cognitive function was not the same for all social classes; there was some evidence of relative cognitive disadvantage (in age 70 IQ and processing speed) with alcohol, but only in those women drinking larger amounts and who belonged to the manual occupational social class groups. In men, the effects of alcohol were less likely to be moderated by social class but were moderated, to some extent, by prior ability. There was a particularly “beneficial” (modifying) effect of wine consumption on cognitive performance (age 70 IQ and verbal ability) in those with a higher childhood IQ. Correspondingly, the association between childhood IQ and cognitive ability in later life was significantly lower among people who drank alcohol than among those who drank little or none.

Moderate alcohol consumption and a preference for wine, in those who are more cognitively able in later life, may be the result of the influence of prior ability and social circumstances on lifestyle factors. Wine drinkers tend to have more favorable health and lifestyle characteristics (e.g., a healthier diet) than predominantly beer and spirits drinkers (Paschall & Lipton, 2005). Given the literature documenting the association between a higher IQ and a healthier lifestyle in large, population-representative samples (Batty, Deary, Schoon, & Gale, 2007), it may be that people with higher cognitive ability engage in a lifestyle that protects against cognitive decline. Here, we found no differences between alcohol consumption groups in the markers of lifestyle that were measured, that is, physical activity and BMI. Further research, perhaps incorporating dietary measures, could evaluate this further.

Study Limitations

Information regarding longer term history of drinking was not available for this dataset, which allowed for previous drinking in the nondrinking group. Ex-drinkers may have very different characteristics from never drinkers (Wannamethee & Shaper, 2002). Compared with lifelong teetotalers, ex-drinkers show higher mortality rates (De Dabry et al., 1992; Shaper & Wannamethee, 2000) and cardiovascular risk factors (Shaper & Wannamethee, 2000). In the LBC1936, nondrinkers had a higher incidence of hypertension, diabetes, high cholesterol, stroke, and cardiovascular disease than moderate to substantial drinkers. Rather than reflecting a health benefit of moderate drinking, these data may reflect ex-drinkers having given up alcohol because of poor physical health.

The FFQ measures alcohol intake from the most recent 2- to 3-month period. Although these short-term data cannot be assumed to reflect habitual patterns of alcohol consumption, a number of reports have supported the validity of this form of measurement, given the temporal stability of patterns of alcohol intake in later

life. For example, Ruitenberg et al. (2002) found that only 6% of older participants reported a change in drinking pattern in the previous 5 years. In this study, classification of alcohol intake into groups was used for illustrative purposes, not for the key analyses. Although this could lead to misclassification, self-reports of alcohol consumption are assumed to be valid for the purpose of classifying drinkers into broad consumption bands (Erens, 1995). Drinkers were classified into consumption groups on the basis of units of alcohol intake, as in previous literature (e.g., Huang, Qiu, Winblad, & Fratiglioni, 2002; Stott et al., 2008). Our method was also consistent with those studies using a three-tiered classification representing nondrinkers, low-level to minimal drinkers (equivalent to one or fewer drinks or 2 units per day), and moderate drinkers (equivalent to more than one drink or 2 units per day; e.g., Britton, Marmot, & Shipley, 2008; Espeland et al., 2006; Lang et al., 2007; McGuire et al., 2007).

The LBC1936 are a somewhat self-selected sample. The sample represents a healthier and more cognitively able subgroup of the original SMS1947 cohort. This healthy survivor effect may have restricted the range of cognitive outcome scores in this study. However, the range of cognitive abilities (and IQ scores) was still large, and a restriction in range of abilities would likely lead to a modest underestimation of the effect sizes.

Study Advantages

All of the participants were born in the same year (1936), thereby eliminating cohort effects and the effects of chronological age. Other studies have been hampered by inadequate cognitive test batteries, limited alcohol measures, and inadequate control for confounders. The LBC1936 study uses a comprehensive battery of cognitive tests. Studies using early life IQ data are rare, and given the stability of IQ across the life span (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman, et al., 2004), the availability of such data offers a unique advantage in the investigation of factors affecting cognition with aging. The FFQ has advantages in terms of ascertaining detailed information on frequency and amount of different sources of alcohol intake, which is often lacking in studies that ask only about overall alcohol intake. Using FFQ data allowed us to look at the associations between different types of alcohol consumption on cognitive abilities, which proved to be important. The associations between alcohol consumption and cognitive domains are not uniform and highlight the importance of making a distinction between alcoholic beverage types during data collection. The cross-sectional nature of this study is a potential limitation, but the LBC1936 study is ongoing. There will be opportunities to follow up with this cohort, offering the potential to investigate alcohol's effects, if any, on cognitive decline.

Conclusions

Our results support the concept that the previously reported moderate alcohol consumption–better cognition association is, substantially, a consequence of confounding by higher prior cognitive ability and adult SES. The exceptions were positive associations between alcohol intake and memory performance and verbal ability. However, the effects were small, and the clinical significance of these findings is uncertain. It is not until we examine

mediating factors such as IQ and SES more fully across the life span that we can begin to examine the two-way nature of the alcohol–cognition relationship.

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Smoking, childhood IQ, and cognitive function in old age

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ABSTRACT

Objectives: To examine the association between smoking history and cognitive function in old age, and whether it remains after controlling for childhood cognitive ability (IQ) and adult socioeconomic status (SES).

Methods: In the Lothian Birth Cohort 1936 Study, 1080 men and women, who previously participated in a nationwide IQ-type test in childhood, were followed up at age 70. The associations between smoking history and age 70 IQ, general cognitive ability (*g*), processing speed, memory, and verbal ability were assessed.

Results: Lower childhood IQ was associated with a higher risk of becoming a smoker and continuing to smoke in late life, and with reduced lung function (FEV1) in late life. Current smokers scored significantly lower than ex-smokers and never smokers on tests of age 70 IQ, general cognitive ability, and processing speed, but not memory or verbal ability. After controlling for childhood IQ and SES, current smoking at age 70 (but not pack years of smoking) was associated with impairments in general cognitive ability and processing speed.

Conclusion: Smoking in old age makes a small, independent contribution to cognitive performance in old age.

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Introduction

Many people continue to smoke into old age despite public health messages warning of the long-term effects on health. Those smokers who survive to old age have an increased risk of significant morbidity [1]. Moreover, a growing body of evidence suggests that smokers perform more poorly in late life on tests of global cognitive function [2,3] and across several cognitive domains, including memory [4–6], information processing speed [4,6], executive function [7] psychomotor speed [8,9] and cognitive flexibility [8], and especially on cognitively demanding tasks [10]. Numerous longitudinal studies have suggested a causal relationship between chronic smoking into late life and an increased risk of cognitive decline and dementia [5,11–14]. Some of these studies propose a dose–response effect of smoking, whereby the degree of cognitive decline experienced increases with the quantity of cigarettes smoked [12,13]. Typically, ex-smokers cognitively outperform those who continue to smoke into old age [4,15].

Several mechanisms have been proposed to explain this relationship. The most widely accepted suggest that cognitive impairment may be due to adverse effects of chronic smoking on cardiac, vascular [11,16] and pulmonary functions [9,17,18]. However, recent findings point to alternative, non-physiological, underlying mechanisms. Firstly, population-based studies have identified an association between prior

intelligence (IQ) and smoking behaviour. People with lower IQ-type scores are more likely to become smokers [19–21]. Those who quit are more likely to have had higher childhood intelligence than those who continue to smoke [22]. Secondly, there is a socioeconomic gradient in smoking prevalence [20,23]. Socioeconomic factors may also explain some of the IQ-smoking relationship [19,24]. A link between prior low IQ and/or low socioeconomic status (SES) and smoking habits may partly explain, by confounding, why long-term smokers perform more poorly on tests of cognition later in life than never-smokers, and why ex-smokers perform better than those who continue to smoke.

Many studies have been unable to rule out prior intelligence (before initiation of smoking) as a potential confounder as this is rarely available when examining cognitive function in older people. Those studies with this data have found that smoking was associated with a small relative decline in cognition after controlling for childhood IQ. However, in one study, the results were based on a single cognitive outcome (verbal reasoning at age 80) and did not control for SES [25]. In the other, of the five cognitive outcomes tested, only psychomotor speed was found to be adversely affected by smoking history (after adjusting for childhood IQ) in a sample of 64-year olds [9]. A 2-year follow-up of the same sample identified a small additional deficit in memory with a positive smoking history [6].

The present study addresses the gaps in the current knowledge of the smoking-cognition relationship in a large sample of older individuals (aged 70), for whom childhood intelligence, later life intelligence and extensive other cognitive data, adult SES, health measures (including lung function), and smoking history are all available. We examine: (1) the association between prior intelligence and smoking history;

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(2) the association between smoking and cognitive function in old age across a wide range of cognitive domains; and (3) the roles of prior intelligence and SES (independently and in combination) in order to evaluate more fully the underlying mechanisms in the smoking-cognition relationship which are as yet, unclear.

Methods

Participants

We examined individuals in the Lothian Birth Cohort 1936 Study (LBC1936) which comprises 1091 men and women. Almost all participants were residents in Edinburgh and the surrounding Lothian region. Early life (mean age 11 years) intelligence test data are available for this sample, because they are surviving participants of the Scottish Mental Survey of 1947 (SMS1947) [26]. Assessment in later life took place between 2004 and 2007 when participants were about 70 years old. Full recruitment and testing procedures are reported in an open-access protocol paper [27]. In brief, the assessment involved an interview, extensive cognitive testing, a physical examination, and questionnaires. Smoking data were available for all 1091 participants in the LBC1936. Eleven participants scored less than 24 on the MMSE; this cut-off is often used to indicate possible dementia. These participants were excluded from statistical analyses. The sample comprised 1080 individuals (539 men). Ethics permission for the LBC1936 Study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland and from Lothian Research Ethics Committee for Scotland. The research was carried out in compliance with the Helsinki Declaration. All participants gave their written, informed consent.

Measurements

Smoking history

Data on smoking history were collected during the interview, including: current smoking status (never, ex or current smokers); the age at which the participants started smoking; age at quitting (for ex-smokers) and; the average number of cigarettes smoked per day. Pack years were calculated as the average number of cigarettes per day times years as a smoker, divided by 20. Pack years expresses life-long exposure to cigarettes.

Moray House Test (ages 11 and 70 MHT IQ)

On June 4th 1947, about 95% of schoolchildren born in 1936 and attending Scottish schools (70,805), took a version of the Moray House Test (MHT) No. 12 (Scottish Council for Research in Education (SCRE)) [28,29]. The MHT is a group-administered test of general intelligence. This test was concurrently validated against the Terman-Merill revision of the Binet scales (SCRE) [29]. SCRE recorded and archived these scores and made them available to the LBC1936 Study. Participants re-sat the MHT at a mean age of 70. MHT scores for the LBC1936 were corrected for age in days at time of testing and converted into IQ-type scores for the sample ($M=100$, $SD=15$).

Other cognitive testing

See Deary et al. for full details [27]. Composite cognitive function scores were used to represent three main cognitive domains. The extraction of these factors, using principal components analysis has been described in detail elsewhere [30,31]. A g factor score, representing general cognitive ability, was derived from scores on six Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III) subtests [32], namely: Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; Symbol Search. A processing speed factor was derived from scores on a set of mental speed measures, namely: Symbol Search (WAIS-III); Digit Symbol (WAIS-III); Simple and Choice Reaction Time mean [33]; Inspection Time (a computer-based test of elementary visual

processing speed) [34]. A memory factor was derived from scores on a set of memory measures from Wechsler Memory Scale-III^{UK} (WMS-III) [35], namely: Logical Memory I immediate and II delayed recall; Spatial Span Forwards and Spatial Span Backwards; Verbal Paired Associates I immediate recall and II delayed recall; and two WAIS-III subtests (Letter-Number Sequencing, Digit Span Backwards). Verbal ability was assessed using the National Adult Reading Test (NART) [36] and the Wechsler Test of Adult Reading (WTAR) [37]. These tests are widely used to estimate prior cognitive ability and each requires the pronunciation of a list of 50 irregular words. The Mini-Mental State Examination (MMSE) is a standardised brief screening measure for cognitive pathology [38]. Scores range from 0 to 30 with a score of less than 24 often used to indicate possible dementia.

Covariates

Sociodemographic

Participants provided general demographic information including marital status and years of full-time education. Adult occupational social class was derived from each participant's highest reported occupation and classified into one of six categories ranging from I (professional occupations) to V (unskilled occupations), with III divided into IIIN (non-manual) and IIIM (manual) [39]. For data analysis, classes IV and V were combined due to the small number of participants in class V.

Health behaviours

Alcohol use was recorded using the Scottish Collaborative Group Food Frequency Questionnaire (FFQ) version 7.0 [40] and expressed as units of alcohol consumed in a typical week. Body Mass Index (BMI) was calculated as weight (kg)/height (m²) from measurements recorded during the physical examination at time of testing. Level of physical activity was obtained from a self-report questionnaire. This measure was coded as follows: 1 – “household chores”; 2 – “walking etc. 1–2 times a week”; 3 – “walking etc. several times a week”; 4 – “exercise 1–2 times a week”; 5 – “exercise several times a week”; and 6 – “keep-fit/heavy exercise/sport several times a week”.

Health measures

Presence or history of hypertension, stroke, cardiovascular disease (CVD) and diabetes were recorded. Serum cholesterol (mmol/L) was measured as part of a blood analysis profile. A measure of lung function (forced expiratory volume in 1 s, FEV1) was obtained using a spirometer. This measure was performed three times and the highest measure was used in the present study.

Statistical analyses

Analyses were performed using IBM SPSS Version 19 (IBM, NY, USA). Lung function measures were converted into percentages of the value predicted from a linear regression of lung function on height for each sex, based on never-smokers. We identified 16 participants' 'pack years' scores as being outliers, which were capped at 100 prior to analysis. We used analysis of variance (ANOVA) and chi-square tests to examine whether demographic and health variables differed between smoking categories. General linear models (GLMs) were used to investigate the associations between cognition at age 70 and smoking status (categorical variable), and cognition at age 70 and pack years (continuous variable), where never smokers were given a score of 0. Cognitive outcomes (dependent variables) were age 70 IQ, g factor, processing speed, memory, and verbal ability (NART and WTAR). Separate models were fitted adjusting for potential confounding variables: age and sex only (model 1); occupational social class (model 2); childhood IQ (model 3); occupational social class and childhood IQ (model 4); lung function (FEV1, model 5); health behaviours (alcohol

use, BMI, physical activity, model 6); and health measures (diabetes, stroke, CVD, model 7). The final, 8th, model included all the covariates mentioned above. All models contained age and sex, except for models containing the outcome age 70 IQ, which is already adjusted for age. We present relevant estimates of effect size, reported here as partial eta-square (η_p^2), and *p* values (the .05 level of significance was used for all data analyses). In examining any attenuation by covariates, of the effect of smoking on cognition at age 70, we draw the reader's attention to the change in effect size, not merely to any change in the significance level.

Results

Descriptive results – participants

Participants' characteristics are summarised in Table 1. At time of testing, 46% reported that they had never smoked, 42% were ex-smokers, and 12% were current smokers. Compared to never smokers, smokers were more likely to be male, unmarried (single, widowed, or divorced), belong to a 'less professional' social class, have fewer years of full-time education, a lower MMSE score, a higher weekly alcohol intake, and a lower BMI. Lung function (FEV1) was lowest in current smokers. Current smokers were more likely to have a history of stroke, CVD or diabetes. Average age at smoking initiation was 18.3 years ($SD=5.43$) for current smokers, and 18.5 ($SD=5.36$) for ex-smokers. Average age at quitting, for ex-smokers, was 46.76 ($SD=13.24$).

Table 1
Characteristics of the study population grouped by smoking status

	Total <i>n</i> =1080 <i>M</i> (<i>SD</i>)	Never smokers <i>n</i> =495 <i>M</i> (<i>SD</i>)	Ex-smokers <i>n</i> =455 <i>M</i> (<i>SD</i>)	Current smokers <i>n</i> =130 <i>M</i> (<i>SD</i>)	<i>p</i>
Pack years ^a	31.4 (27.7)	0	27.9 (28.3)	43.8 (21.2)	
Sociodemographic measures					
Age, years	69.5 (0.83)	69.5 (0.84)	69.6 (0.85)	69.5 (0.74)	
Men %	49.9	40.4	58.4	52.9	<.001
Married %	71.2	71.9	73.6	60.9	.001
Social class %					<.001
I	17.5	18.6	18.8	9.4	
II	36.9	38.3	38.6	26.8	
IIIN	22.8	26	16.8	31.9	
IIIM	17.0	13.5	18.8	23.2	
IV+V	3.8	2.5	4.2	6.5	
Education, years mean (<i>SD</i>)	10.8 (1.1)	10.9 (1.2)	10.7 (1.1)	10.5 (0.95)	.001
MMSE	28.9 (1.3)	29.0 (1.3)	28.8 (1.3)	28.6 (1.3)	.029
Health behaviours					
Alcohol use, U/wk	10.6 (14.2)	8.2 (12.3)	12.6 (14.4)	12.2 (18.5)	<.001
Body Mass Index	27.8 (4.4)	27.6 (4.2)	28.5 (4.4)	26.1 (4.7)	<.001
Physical activity (level)	7.6 (8.1)	7.8 (7.8)	8.0 (8.4)	5.6 (8.3)	.027
Health measures					
Diabetes (%)	8.1	5.7	10.7	8	.026
Stroke (%)	4.9	3.8	4.7	9.4	.014
Cardiovascular disease (%)	24.6	20.7	28.6	24.6	.046
Cholesterol mmol/l	5.5 (1.2)	5.6 (1.2)	5.3 (1.2)	5.5, (1.2)	.011
Lung function measure					
FEV1	2.4 (0.69)	2.4 (0.65)	2.4 (0.69)	2.0 (0.70)	<.001
%FEV1 ^b	94.4	100.1	92.6	75.6	

Note.
MMSE – Mini-Mental State Examination; FEV1 – forced expiratory volume in 1 s.
p values are from t-tests, ANOVA and chi-square tests as appropriate.
^a Pack years was calculated by dividing the average number of cigarettes smoked daily by 20 and then multiplying that by the number of years smoked.
^b % Values refer to percentage of values predicted by sex and height in never-smokers.

Table 2
Cognitive outcomes by smoking status (ANOVA)

	Never smokers <i>n</i> =495 <i>M</i> (<i>SD</i>)	Ex-smokers <i>n</i> =455 <i>M</i> (<i>SD</i>)	Current smokers <i>n</i> =130 <i>M</i> (<i>SD</i>)	<i>p</i>
Age 11 IQ ^a	101.4 (14.9)	99.3 (14.8)	98.2 (14.7)	.036
Age 70 IQ ^a	101.5 (13.4)	100.5 (14.7)	96.0 (16.0)	<.001
<i>g</i> Factor	0.11 (0.97)	0.02 (0.99)	−0.32 (0.93)	<.001
Processing speed	0.10 (0.97)	0.03 (0.98)	−0.34 (0.94)	<.001
Memory	0.04 (0.97)	0.04 (0.97)	−0.18 (1.04)	.063
NART	34.9 (8.0)	34.6 (8.1)	33.2 (8.2)	.120
WTAR	41.4 (6.9)	41.2 (7.2)	40.0 (6.9)	.136

Note.

^a Age 11 IQ and age 70 IQ are derived from scores on the Moray House Test and converted to standard IQ type scores ($M=100$, $SD=15$).

Current smoking status and cognitive function

Table 2 presents IQ-type scores (at ages 11 and 70) and other cognitive function scores by smoking status. These unadjusted results showed a significant association between smoking status and IQ at age 11 ($p=.036$) and age 70 ($p<.001$). Age 11 IQ scores were significantly lower in current smokers compared to never smokers (by 3.2 points), with an intermediate score in ex-smokers. At age 70, current smokers had a 5.5 point IQ disadvantage compared to never-smokers. Smokers also performed significantly worse than never smokers on tests of general cognitive ability (*g* factor) ($p<.001$) and processing

Table 3General linear models of associations between smoking status and cognitive outcomes at age 70 (*p* values and associated partial eta squared values)

Models	Age 70 IQ ^a		g Factor		Processing speed		Memory		NART		WTAR	
	<i>n</i> = 1069		<i>n</i> = 1062		<i>n</i> = 1028		<i>n</i> = 1037		<i>n</i> = 1078		<i>n</i> = 1078	
	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2
1. A+S	<.001	.012	<.001	.016	.009	.015	.202	.002	.120	.002	.125	.002
2. A+S+SC	.029	.005	.004	.008	.003	.009	.852	.000	.987	.000	.973	.000
3. A+S+IQ11	.057	.004	.002	.010	.006	.008	.964	.000	.488	.000	.474	.001
4. A+S+SC+IQ11	.205	.002	.011	.007	.019	.006	.763	.000	.179	.002	.198	.002
5. A+S+FEV1	.068	.003	.041	.004	.056	.004	.852	.000	.943	.000	.597	.000
6. A+S+HB	<.001	.015	<.001	.017	<.001	.015	.133	.002	.043	.004	.062	.004
7. A+S+HM	<.001	.011	<.001	.014	<.001	.012	.208	.002	.133	.002	.148	.002
8. ALL	.550	.000	.329	.001	.379	.001	.626	.000	.285	.001	.329	.001

Note.

Pack years of smoking were capped at 100 (*n* = 16 outliers were recoded as 100).

A – age; S – sex; SC – occupational social class; IQ11 – age 11 IQ; FEV1 – forced expiratory volume in 1 s; HB – health behaviours (alcohol units/wk, BMI, physical activity level); HM – health measures (diabetes, stroke, CVD); and ALL – all covariates.

p values in bold represent significant negative associations between smoking status and cognitive outcome (*p* < .05).^a Age 70 IQ is already age-adjusted (age not included in the models for this outcome variable).

speed (*p* < .001), but not memory or verbal ability (NART and WTAR). Table 3 shows the results of GLMs used to examine the association between smoking status and cognitive outcomes at age 70. In the age- and sex-adjusted only model (model 1), smoking status was associated with significantly lower scores on tests of age 70 IQ (η_p^2 = .012), *g* factor (η_p^2 = .016), and processing speed (η_p^2 = .015). After adjusting for social class and age 11 IQ independently and in combination (models 2, 3 and 4), the association between smoking and age 70 IQ ceased to be significant. The associations between smoking status and general cognitive ability and processing speed remained significant after controlling for both age 11 IQ and social class (independently and in combination), although the effect sizes were slightly attenuated (see model 4: *g* factor η_p^2 = .007; processing speed η_p^2 = .006). These associations persisted (with the exception of model 5 for processing speed, which narrowly missed significance after controlling for FEV1) until full adjustment for all covariates (model 8). Further GLMs (data available on request) confirmed that these results were driven by significant differences between current smokers and non-current smokers, rather than between ever- and never-smokers.

Lifetime smoking (pack years) and cognitive function

Pack years of smoking was negatively correlated with age 11 IQ (r = -.12, *p* < .001). A separate set of GLMs were used to examine the

association between pack years and cognitive outcomes at age 70, and the effects of potential confounders on these associations (see Table 4). In the age- and sex-adjusted only model (model 1), increasing pack years was associated with significantly lower scores on tests of age 70 IQ (η_p^2 = .017), *g* factor (η_p^2 = .018), processing speed (η_p^2 = .017), and verbal ability (NART η_p^2 = .008; WTAR η_p^2 = .007). After adjusting for social class and age 11 IQ separately (models 2 and 3), the significant associations between pack years and age 70 IQ (model 2; η_p^2 = .006, model 3; η_p^2 = .004) *g* factor (model 2; η_p^2 = .005, model 3; η_p^2 = .007) and processing speed (model 2; η_p^2 = .004, model 3; η_p^2 = .007) remained, but the effect sizes were markedly attenuated. After adjustment for social class and age 11 IQ in combination (model 4), there were no significant associations between lifetime smoking and cognitive abilities. Controlling for FEV1 (model 5) also removed significant associations between smoking and cognitive abilities, with the exception of age 70 IQ (*p* = .030). It should be noted, however, that FEV1 correlated significantly with age 11 IQ (r = .159, *p* < .001). Adjustment for health behaviours (model 6) or health measures (model 7) caused no attenuation of the effect of smoking on cognitive functions that was found in the sex and age-adjusted model (model 1). With full adjustment (model 8), there were no significant effects of lifetime smoking on cognitive abilities.

We also examined the effect of pack years in current smokers only and found no dose–response effect of smoking for any of the cognitive

Table 4General linear models of associations between pack years of smoking (lifetime smoking) and cognitive outcomes at age 70 (*p* values and associated partial eta squared values)

Models	Age 70 IQ ^a		g Factor		Processing speed		Memory		NART		WTAR	
	<i>n</i> = 1069		<i>n</i> = 1062		<i>n</i> = 1028		<i>n</i> = 1037		<i>n</i> = 1078		<i>n</i> = 1078	
	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2	<i>p</i>	η_p^2
1. A+S	<.001	.017	<.001	.018	<.001	.017	.104	.003	.004	.008	.006	.007
2. A+S+SC	.015	.006	.022	.005	.038	.004	.931	.000	.439	.001	.450	.001
3. A+S+IQ11	.035	.004	.007	.007	.008	.007	.765	.000	.829	.000	.829	.000
4. A+S+SC+IQ11	.163	.002	.122	.002	.214	.002	.315	.001	.554	.000	.628	.000
5. A+S+FEV1	.030	.004	.067	.003	.091	.003	.712	.000	.402	.001	.495	.000
6. A+S+HB	<.001	.013	.002	.010	.003	.010	.317	.001	.084	.003	.138	.002
7. A+S+HM	<.001	.015	<.001	.014	<.001	.012	.113	.002	.006	.007	.009	.006
8. ALL	.231	.002	.895	.000	.713	.000	.536	.000	.481	.000	.602	.000

Note.

Pack years of smoking were capped at 100 (*n* = 16 outliers were recoded as 100).

A – age; S – sex; SC – occupational social class; IQ11 – age 11 IQ; FEV1 – forced expiratory volume in 1 s; HB – health behaviours (alcohol units/wk, BMI, physical activity level); HM – health measures (diabetes, stroke, CVD); and ALL – all covariates.

p values in bold represent significant negative associations between pack years of smoking and cognitive outcome.^a Age 70 IQ is already age-adjusted (age not included in the models for this outcome variable).

outcomes tested at age 70. The correlation between pack years of smoking in current smokers and age 70 IQ is $r=.038$ ($p=.668$) and between pack years of smoking and general (g) cognitive ability is $r=.093$ ($p=.296$). We also ranked smokers into quintiles of pack years; as before, there were no significant associations between pack years and any of the cognitive outcomes. On examination of the means plots, there was no trend to suggest that such a relationship exists.

Discussion

We examined a sample of individuals, aged about 70, for whom childhood intelligence scores are available. We replicated previous findings that lower IQ at age 11 was associated with a higher risk of becoming a smoker and continuing to smoke into old age, and with the amount of cigarettes smoked over the lifespan. We found an adverse effect of current smoking on general cognitive ability (g) and information processing speed – but not memory or verbal ability – even after controlling for childhood IQ and SES. We found an effect of pack years of smoking on cognitive function of those who had smoked more over their lifetime, which was non-significant after controlling for their (lower) IQ scores and SES. In this sample, current smoking makes a small, negative contribution to cognitive ability level in old age. However, a novel finding was that the observed associations between cumulative smoking (pack years) and poorer cognitive function scores in old age were accounted for, largely, by variations in prior cognitive ability and SES, not independently, but in combination.

Childhood IQ and adult smoking behaviour

The first objective of the study was to examine the relationship between childhood IQ and smoking behaviour in adulthood. Our results are consistent with previous studies showing that IQ predicts onset and cessation of smoking. In a cohort born in 1921, Taylor et al. reported that age 11 IQ predicted cessation, but not uptake of smoking [22], perhaps reflecting social attitudes to tobacco over a particular historical period. Batty et al. found that a higher IQ at age 10 was associated with a reduced prevalence of current smoking and an increased likelihood of having given up smoking by midlife [19]. The conclusion often drawn from the body of literature supporting a link between IQ and smoking behaviour is that IQ influences differential valuations of the health consequences of smoking [41], as well as access to smoking cessation programmes, via social background [42].

Interestingly, we identified a link between lower childhood IQ and poorer adult lung function, consistent with the work of Richards et al. [17] and Deary et al. [43]. They reported a link between childhood intelligence and FEV1 in later life, even after controlling for lifetime smoking. They proposed that respiration and mental functions may be subject to the same physiological processes and are a function of what has been termed general bodily system integrity [44].

Smoking and cognitive function at age 70

Our second objective was to examine the association between smoking and cognitive function across a range of cognitive domains. General cognitive ability (g) and processing speed were lower in current smokers at age 70, than never- and ex-smokers. These results are in keeping with other studies reporting cognitive impairment in old age with long-term smoking [11]. The relationship between current smoking and poorer cognitive function remained after controlling for markers of ill-health, health behaviours and lung function (FEV1). However, despite having made an especially thorough assessment of memory, we found no effect of smoking on memory function, in contrast to some other studies [4,6,12,14].

Past smoking was not associated with significantly poorer performance than never smokers in any cognitive domain. Deary et al. found

that current smokers, but not ex-smokers, had lower IQ scores at age 80 (after adjusting for childhood IQ) when compared with lifelong never-smokers [25]. This suggests that cognitive detriments, albeit small, may only occur after prolonged exposure to cigarettes over the course of a lifetime. However, a 24-month smoking cessation trial using an old age sample (>68 years), showed that unsuccessful quitters over this 2-year period scored significantly worse on cognitive tests than successful quitters and non-smokers [15]. Therefore, quitting smoking, at any stage in adulthood, may be beneficial to cognitive health in later years. Given that pack years of smoking ceased to be associated with cognitive performance in the present study, after controlling for childhood IQ and SES, it may be that smoking in old age, irrespective of previous smoking history, affects cognitive health at a time when the body is most vulnerable to its adverse, systemic, and physiological effects.

Childhood IQ and SES as confounders in the smoking–cognitive function relationship

Our final objective was to investigate the roles of childhood IQ and SES in the smoking–cognition relationship. There is a high level of stability in cognitive function across most of the lifespan; childhood IQ accounts for about half the variance observed in later life [45]. In this sample, the raw correlation (r) between age 11 and age 70 IQ is .69, $p<.001$. Controlling for age 11 IQ and SES attenuated the relationship between smoking status and cognitive function and reduces to non-significance the association between lifetime smoking and cognitive function. A contribution of SES was predicted given that 1) it is a correlate of IQ, and 2) smoking was less common among participants from higher (more professional) social classes, a finding documented by other studies in the area [19,23]. Controlling for sociodemographic variables was found to completely attenuate the observed association between lung function and cognitive function in a large sample of men and women in early old age [46]. It has been proposed that lower intelligence among lower socioeconomic groups leads to a poorer understanding of the negative health consequences of health-risk behaviours such as smoking [47]. The inability to give up smoking may also be related to poorer SES as a result of lower job attainment and financial strains [48].

Strengths and limitations

The major strength of this study was the availability of IQ data at two distant time points (age 11 and age 70) derived from scores on a validated test of general intelligence (the MHT). We were able to examine the contribution of smoking to relative cognitive change on this measure from childhood to late adulthood. There was a further advantage of examining childhood cognitive ability before the majority (98.5%) had begun smoking. We studied a cohort who shares the same year of birth. The narrow age cohort is an important design advantage given that smoking patterns change over time, and because chronological age itself makes a large contribution to cognitive functions and health in old age [49]. We had comprehensive cognitive data with multiple tests of important cognitive domains at age 70. We had data on quantity and duration of smoking in addition to current smoking status. The LBC1936 sample has data on a wide variety of sociodemographic and health factors. This made it possible to adjust for a range of potential confounders.

The study has some limitations. Although the use of a narrow age group is advantageous, we note that this limits the generalisability of results. Second, self-reported smoking history is open to recall bias, especially among elderly participants. Under-reporting of smoking history may be a potential confounder of the data. It should be noted that, if the direction of this effect was such that people with greater cognitive declines were more likely to under-report smoking history, then the effect sizes in this report would be under-estimates. However, self-reported smoking has high agreement with serum cotinine measures [50]. Third, the LBC1936 is a self-selecting, volunteer sample and, as such, and is typically more cognitively able and healthier than the

general population. The LBC1936 achieved higher mean age 11 cognitive scores ($M=49.0$, $SD=11.8$) than both the nationwide and Edinburgh SMS1947 average ($M=36.7$, $SD=16.1$, $M=40.3$, $SD=15.5$, respectively) and this may have restricted the range of cognitive outcome scores in the study. That said, the range of age 11 cognitive scores in the current sample was still large ($M=49.1$, $SD=11.7$). The most likely result of this is some small underestimation of effect sizes of the associations reported here. Smoking is associated with higher morbidity and mortality rates. Of the smokers who survive to old age, those with significant health problems are less likely to participate in such a study, possibly leading to an under-representation of smokers in the current sample.

In conclusion, our results suggest that smoking in old age may contribute to age-related cognitive impairments in general cognitive ability (g) and speed of information processing. Some of the apparent cognitive impairment due to lifetime smoking can be accounted for by a lower childhood cognitive ability and socioeconomic status. Cessation of smoking in adulthood appears to 'buffer' the cognitive ageing experienced by those who continue to smoke. In terms of public health implications, the present findings suggest that there are cognitive benefits to quitting smoking, even for older adults who have been smoking for many years; intervention programmes should target smokers at all ages.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

JC performed the analyses and led the writing of the article. JC and AG were involved in data collection. AG, JS and ID contributed to the study design, interpretation of analysis and drafting of the manuscript.

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Do dietary patterns influence cognitive function in old age?

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ABSTRACT

Background: Evidence from observational studies to date suggests that healthy dietary patterns are associated with better cognitive performance in later life. We examined the extent to which childhood intelligence quotient (IQ) and socioeconomic status account for this association.

Methods: Analyses were carried out on 882 participants in the Lothian Birth Cohort 1936 Study. Four dietary patterns were extracted using principal components analysis of a food frequency questionnaire, namely “Mediterranean-style,” “health aware,” “traditional,” and “sweet foods.” Cognitive function was assessed at the age of 70 years, including general (*g*) cognitive ability, processing speed, memory, and verbal ability.

Results: Before adjustment for childhood IQ and socioeconomic status, the “Mediterranean-style” dietary pattern was associated with significantly better cognitive performance (effect size as partial eta-square (η_p^2) range = 0.005 to 0.055), and the “traditional” dietary pattern was associated with poorer performance on all cognitive domains measured in old age (η_p^2 = 0.009 to 0.103). After adjustment for childhood IQ (measured at the age of 11 years) and socioeconomic status, statistical significance was lost for most associations, with the exception of verbal ability and the “Mediterranean-style” pattern (National Adult Reading Test (NART) η_p^2 = 0.006 and Wechsler Test of Adult Reading (WTAR) η_p^2 = 0.013), and the “traditional” pattern (NART η_p^2 = 0.035 and WTAR η_p^2 = 0.027).

Conclusions: Our results suggest a pattern of reverse causation or confounding; a higher childhood cognitive ability (and adult socioeconomic status) predicts adherence to a “healthy” diet and better cognitive performance in old age. Our models show no direct link between diet and cognitive performance in old age; instead they are related via the lifelong-stable trait of intelligence.

Key words: dietary patterns, childhood intelligence (IQ), cognitive aging

Introduction

The role of diet and nutritional factors in brain aging is attracting much research attention. A growing body of evidence links dietary patterns with cognitive abilities in old age. Evidence from observational studies suggests that a “healthy” diet is associated with better cognitive function. Some studies employed an *a priori* (hypothesis-based) approach to show that degree of adherence to a pre-defined “healthy” diet (using diet quality indices) was related to cognitive function in older individuals (Huijbregts *et al.*, 1998; Wengreen *et al.*, 2009), although these studies used only a brief and limited measure of global cognition, the Mini-Mental

State Examination (MMSE). By contrast, one study reported a lack of association (Shatenstein *et al.*, 2012). However, the *a priori* method makes assumptions about which specific food items constitute a healthy diet based on current nutritional research and does not take into account the complexity of the full diet (Allès *et al.*, 2012). Only three studies, to our knowledge, have investigated the effects of overall dietary patterns, extracted *a posteriori* (based on correlations among all dietary components), on cognitive outcomes in healthy, old age populations. One study reported better cognitive performance (using the MMSE only) among the “healthy” dietary pattern, characterized by a higher intake of fruit, vegetables, and fish (Samieri *et al.*, 2008). Studies using more comprehensive neuropsychometric tests assessing specific cognitive domains are limited (Akbaraly *et al.*, 2011; Kesse-Guyot *et al.*, 2012). In one study the “healthy” pattern was associated with better global cognitive function and verbal memory

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than the “traditional” pattern (Kesse-Guyot *et al.*, 2012). In the other study, the observed associations between the “healthy” or “whole food” pattern and decreased odds of cognitive deficit on all cognitive tests (compared with the “processed” food pattern) in a sample of 60-year-old individuals were significantly attenuated by education (Akbaraly *et al.*, 2011).

With this attenuation of a potentially important association in mind, and given that individual differences in cognitive abilities from youth strongly predict cognitive ability differences in old age (Gow *et al.*, 2011), and the adoption of health behaviors in adulthood (Batty *et al.*, 2007; Anstey *et al.*, 2009), it is plausible that the link between dietary patterns and cognitive performance is not causal. Rather, this association seen in observational studies could reflect a lifelong trait association between cognitive ability and diet choice. Education is sometimes used as a proxy measure for both prior cognitive ability and social background (Deary and Johnson, 2010), but no study to date has been able to control for prior cognition. Without a valid measure of early-life cognitive ability we cannot properly examine the extent to which diet influences cognition in old age, or conclude that adhering to a particular diet contributes to successful cognitive aging.

In the present study we investigate the extent to which prior cognitive ability (measured at the age of 11 years) and adult socioeconomic status (SES; assessed by occupation) account for the association between healthy dietary patterns and better cognitive functions in old age. The present study uses an *a posteriori* method of extracting dietary patterns.

Methods

Study population

The study sample was drawn from the Lothian Birth Cohort 1936 Study (LBC1936), an ongoing longitudinal study of cognitive aging, which comprises 1,091 men and women living independently in the community. Almost all participants were residing in Edinburgh and the surrounding Lothian region at recruitment. Early-life (mean (M) age 11 years) intelligence test data are available for this sample because most are surviving participants of the Scottish Mental Survey of 1947 (SMS1947; Deary *et al.*, 2009). Assessment in later life took place between 2004 and 2007 when participants were aged about 70 years ($M = 69.5 \pm 0.8$). Full recruitment and testing procedures are reported in an open-access protocol paper (Deary *et al.*, 2007). In brief, the assessment involved an interview, extensive cognitive testing, a physical examination, and questionnaires. Food frequency questionnaire (FFQ) data

were available for 882 participants. Persons scoring <24 on the MMSE ($n = 4$) were excluded; using this cut-off reduces the risk of having persons with dementia in the sample. After exclusions, 878 persons remained for analyses. Ethics permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from the Lothian Research Ethics Committee for Scotland (LREC/2003/2/29). The research was carried out in compliance with the Helsinki Declaration. All participants gave their written, informed consent.

Dietary assessment

Dietary patterns were assessed using the Scottish Collaborative Group FFQ version 7.0. The FFQ version 7.0 lists 168 foods or drinks and a common unit or portion size for each item is specified. Response to all items was on a 9-point scale, ranging from “rarely or never” to “7+ per day” in the previous two to three months. All participants ($n = 1,091$) were asked to complete the FFQ at home and return it by post. Of these questionnaires, 98 were not returned, 26 were returned blank, and 39 had >10 missing items and excluded from the analyses. A further 46 questionnaires were excluded due to having extreme energy intakes, defined as <2.5 th or >97.5 th centile for energy intake.

Identification of dietary patterns

Dietary factors were previously identified for this sample using principal components analysis (PCA) with varimax orthogonal rotation on all the FFQ items. Further details can be found in Möttus *et al.* (2011). Four main components were extracted, based on the examination of scree plots, which accounted for 11.67% of the total variance. Component scores were calculated using food items with factor loadings exceeding 0.30. The four components were labeled according to the types of foods with the highest factor loadings. The factor loadings of specific food items on each of the four dietary patterns identified are available as supplementary data (see Table S1 published as supplementary material online attached to the electronic version of this paper at <http://journals.cambridge.org/ipg>). A “Mediterranean-style” diet pattern (22 items) was defined by greater consumption of vegetables (such as leeks or courgettes, broccoli, salad vegetables) and also had positive loadings from fish, poultry, pasta, rice, water, tomato-based sauces, oil and vinegar dressing, and beans. The “health aware” diet pattern (14 items) was defined by eating more fruits (such as apples, bananas, tinned fruit, oranges, and others) and carrots, and had negative loadings from high consumption of meat products (bacon or

gammon, pork or lamb, and sausages) eggs, and spirits or liqueurs. Both components essentially identified “healthy” dietary patterns. A “traditional” diet (ten items) was defined as eating more tinned vegetables, peas or beans, carrots, baked beans, bottled sauces, meat or chicken pies, pasties and sausage rolls, mashed potatoes, custard or other sweet sauces, milk-based puddings, and drinking less filter, espresso, or cappuccino coffee. This component identified a traditional Scottish dietary pattern, low in fruit and salad vegetables. The final component, a “sweet foods” diet (17 items), was defined as eating more puddings, cakes, biscuits, and chocolate. Factor scores were calculated by summing the frequency of consumption multiplied by factor loadings across all food items. In this way, each individual gets score values for each of the identified dietary patterns, indicating the degree to which the individual’s diet conforms to the dietary pattern.

Cognitive assessment

MORAY HOUSE TEST (AGE 11 AND 70 MHT IQ)

On 4 June 1947, about 95% of schoolchildren born in 1936 and attending Scottish schools (70,805) took a version of the Moray House Test (MHT) No. 12 (Scottish Council for Research in Education (SCRE), 1933; 1949). The MHT is a group-administered test of general intelligence. This test was concurrently validated against the Terman–Merrill revision of the Binet scales (SCRE, 1949). SCRE recorded and archived these scores and made them available to the LBC1936 study. Participants re-sat the MHT at a mean age of 70 years. MHT scores for the LBC1936 study were corrected for age in days at the time of testing and converted into intelligence quotient (IQ)-type scores for the sample ($M = 100$, $SD = 15$).

OTHER COGNITIVE TESTING

Three cognitive domains are represented in the LBC1936 cognitive battery: general (g) cognitive ability, processing speed, and memory. The derivation of these factors by PCA has been described elsewhere (Luciano *et al.*, 2009; Corley *et al.*, 2010a). A general (g) cognitive ability factor was derived from scores on six Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III) subtests (Wechsler, 1998a), namely Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; and Symbol Search. A general (g) cognitive ability factor is well established in the literature (Deary *et al.*, 2010). A processing speed factor was derived from scores on a set of mental speed measures, namely Symbol Search (WAIS-

III); Digit Symbol (WAIS-III); Simple and Choice Reaction Time mean (Cox *et al.*, 1993; Deary *et al.*, 2001); and Inspection Time (a computer-based test of elementary visual processing speed; Deary *et al.*, 2004a). A memory factor was derived from scores on a set of memory measures from Wechsler Memory Scale-III^{UK} (Wechsler, 1998b), namely Logical Memory I immediate recall and II delayed recall; Spatial Span Forwards and Spatial Span Backwards; Verbal Paired Associates I immediate recall and II delayed recall; and two WAIS-III subtests (Letter-Number Sequencing, and Digit Span Backwards). Verbal ability was assessed using the National Adult Reading Test (NART; Nelson and Willison, 1991) and the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001). These tests are widely used to estimate prior cognitive ability and each requires the pronunciation of a list of 50 irregular words. The MMSE is a standardized brief screening measure for cognitive pathology (Folstein *et al.*, 1975). Scores range from 0–30, with a score of <24 often used to indicate possible dementia.

Covariates

Covariates included age (in days at the time of testing) and sex. Adult SES was derived from participants’ (or their spouses’) highest reported occupation and classified into one of the following six categories: professional; managerial; skilled non-manual; skilled manual; semi-skilled; and unskilled (Office of Population Censuses and Surveys, 1980). For data analysis, classes 4 and 5 (semi-skilled and unskilled) were combined due to the small number of participants ($n = 4$) in class V. Age 11 IQ was derived from scores on the MHT, which participants sat for the SMS1947, as mentioned above. Raw scores were corrected for age in days at the time of testing and converted into IQ-type scores for the sample ($M = 100$, $SD = 15$).

Participants were also asked questions about their alcohol consumption (units per week); smoking (converted to pack years); and physical activity (coded as follows: 1 – “household chores”; 2 – “walking etc. 1–2 times a week”; 3 – “walking etc. several times a week”; 4 – “exercise 1–2 times a week”; 5 – “exercise several times a week”; 6 – “keep-fit/heavy exercise/sport several times a week”). Health measures included history of diabetes, stroke, or cardiovascular disease (CVD) (all coded as dichotomous variables, yes/no).

Statistical analysis

Analyses were performed using SPSS version 19 (IBM, NY, USA). We screened the data for

outliers and excluded those individuals whose scores were greater than 3.5 SD from the sample mean for each dietary pattern: “Mediterranean-style” ($n = 5$); “health aware” ($n = 6$); “traditional” ($n = 7$); and “sweet” ($n = 7$). Classification of dietary patterns into tertiles was used to illustrate any demographic, dietary, and health differences within the patterns. We used one-way analysis of variance (ANOVA) for continuous variables, and Chi-square tests (χ^2) for categorical variables, to examine the relations between dietary patterns and characteristics of the participants. We report the p -value for trend. The main analyses examined the effects of dietary pattern scores, as continuous variables, and cognitive functions at age 70. For these analyses, we used a General Linear Model (GLM) approach in a series of models; each subsequent model was adjusted for a different set of covariates. All models contained age and sex. Model 2 added SES. Model 3 added age 11 IQ. Model 4 added SES and age 11 IQ. We report p -values ($p < 0.05$ as level of significance was used for all data analyses). We present relevant estimates of effect size, reported here as partial eta-square (η_p^2): η_p^2 is the proportion of the total variance attributable to a given factor. It is defined as the ratio of variance in the outcome accounted for by an effect, and that effect plus its associated error variance, within an ANOVA/GLM design.

Results

Table 1 shows the characteristics of study participants in relation to dietary patterns. Individuals with higher scores on the “Mediterranean-style” pattern were significantly younger, less deprived, belonged to a more professional social class, had more years of education and a higher age 11 IQ, consumed more alcohol, smoked less (in pack years), and were more physically active. Those with higher scores on the “traditional” pattern were significantly more likely to be males, older, have fewer years of education and a lower age 11 IQ, a higher body mass index (BMI), belong to a less professional social class, smoke more, and report less physical activity. In addition, those with more traditional diets had a lower prevalence of high (total) cholesterol. Those with higher scores on the “health aware” pattern were more likely to be females, belong to a less professional social class, smoke less and drink less alcohol, and have a lower BMI. Individuals with higher scores on the “sweet foods” pattern were more likely to have more years of education, a higher MMSE score, drink less alcohol, and have a lower BMI.

Dietary patterns and early-life cognitive ability

Table 2 shows the associations between dietary patterns and early-life cognitive ability (age 11 IQ). Higher scores on the “Mediterranean-style” pattern were associated with higher childhood IQ scores ($p < 0.001$). Between the lower and upper tertiles, there was an IQ difference of 5 points. Higher scores on the “traditional” dietary pattern ($p < 0.001$) were associated with lower childhood IQ scores; there was an IQ difference of 8.2 points between the lower and upper tertiles. There was no significant difference in childhood IQ scores between tertiles of the “health aware” and “sweet foods” dietary patterns.

Dietary patterns and late-life cognitive ability

Table 3 presents the associations between dietary pattern scores (as continuous variables) and cognitive abilities at a mean age of 70 years. General linear models controlled for a different set of covariates at each stage (model). In the basic age- and sex-adjusted only model (model 1), the “Mediterranean-style” pattern was associated with significantly higher scores on all cognitive domains at age 70 (η_p^2 range 0.005 to 0.055). The “traditional” pattern was associated with significantly lower scores on all cognitive domains at age 70, most at $p < 0.001$ (η_p^2 range 0.028 to 0.10), and processing speed ($p = 0.007$ $\eta_p^2 = 0.009$). The magnitude of the relationships was stronger for verbal ability tests. The “health aware” pattern was associated with lower age 70 IQ scores. The “sweet foods” pattern was associated with higher scores on age 70 IQ, general (g) cognitive ability, and one of the verbal ability measures (WTAR). The range of effect sizes for the latter two dietary patterns was significantly smaller.

Generally, controlling for age 11 IQ and occupational social class (models 2, 3, and 4) strongly attenuated most of the associations between the dietary patterns and cognitive scores, and often reduced them to non-significance. These key results illustrate the significant roles that premorbid cognition and adult SES play in shaping the relationship between diet and cognition. For example, with only age and sex in the model it would appear that the “Mediterranean-style” diet accounts for 2.7% of the variation in age 70 IQ score. After adding, separately, occupational social class and age 11 IQ scores as covariates, this reduces to 0.3%, a marked attenuation. In the multivariable model that included age, sex, age 11 IQ, and occupational social class (model 4), only the relation of the “Mediterranean-style” pattern with the verbal ability measures remained statistically significant. However, the effect

Table 1. Characteristics of the sample as a function of dietary pattern scores at age 70

	MEDITERRANEAN-STYLE PATTERN				TRADITIONAL PATTERN			
	LOWER TERTILE	MIDDLE TERTILE	UPPER TERTILE	p	LOWER TERTILE	MIDDLE TERTILE	UPPER TERTILE	p
Demographic factors								
Age, years (M ± SD)	69.6 ± 0.8	69.5 ± 0.8	69.4 ± 0.8	0.007	69.3 ± 0.8	69.6 ± 0.8	69.6 ± 0.8	0.001
Women (%)	47.6	52.4	44.5	0.167	62.4	50.3	43.4	< 0.001
Social class (%)				< 0.001				< 0.001
1	7.8	20.5	26.7		28.5	14.5	12.4	
2	31.9	39.9	44.6		45.1	39.2	32.3	
3	30.1	23.3	18.6		20.8	25.1	26.2	
3.5	25.2	14.2	7.7		5.2	18.7	23.0	
4 + 5	5.0	2.1	2.5		0.34	2.5	6.0	
SIMD score (M ± SD)	4,305 ± 1,935	5,049 ± 5,857	6,805 ± 12,463	0.001	5,669 ± 5,744	5,579 ± 9,839	4,954 ± 8,179	0.512
Education, years (M ± SD)	10.5 ± 0.9	10.8 ± 1.1	11.1 ± 1.2	< 0.001	11.2 ± 1.2	10.6 ± 1.1	10.6 ± 1.0	< 0.001
Age 11 IQ (M ± SD)	98.5 ± 13.0	102.0 ± 14.5	103.5 ± 14.0	< 0.001	106.4 ± 12.4	99.9 ± 13.0	98.2 ± 15.0	< 0.001
MMSE score (M ± SD)	28.9 ± 1.3	28.9 ± 1.2	29.1 ± 1.2	0.221	29.1 ± 1.1	28.9 ± 1.3	28.9 ± 1.2	0.145
Health behavior								
Alcohol, units/week (M ± SD)	7.9 ± 15.1	10.7 ± 13.7	12.8 ± 12.9	< 0.001	12.0 ± 12.9	10.2 ± 14.2	9.6 ± 14.9	0.104
BMI (M ± SD)	27.7 ± 4.2	27.5 ± 4.2	27.4 ± 4.1	0.661	26.8 ± 4.1	27.6 ± 4.1	28.2 ± 4.2	< 0.001
Physical activity, level (M ± SD)	2.8 ± 1.1	3.0 ± 1.1	3.2 ± 1.1	< 0.001	3.1 ± 1.1	3.0 ± 1.1	2.9 ± 1.0	0.033
Smoking, pack years (M ± SD)	31.4 ± 29.9	24.9 ± 25.5	22.2 ± 21.0	0.018	21.1 ± 22.0	24.5 ± 22.1	31.7 ± 30.6	0.004
Dietary factors								
Energy (kcal/day) (M ± SD)	1,694 ± 477	1,857 ± 490	2,100 ± 550	< 0.001	1,701 ± 465.7	1,791 ± 476.5	2,153 ± 537.3	< 0.001
Sugars (g/day) (M ± SD)	106.5 ± 43.2	110.9 ± 44.7	123.5 ± 49.1	< 0.001	102.9 ± 39.2	107.6 ± 41.5	128.9 ± 50.3	< 0.001
Vitamin C (g/day) (M ± SD)	78.9 ± 39.0	100.2 ± 44.2	137.3 ± 67.8	< 0.001	104.8 ± 50.6	99.9 ± 59.4	114.0 ± 66.3	0.014
Fiber (g/day) (M ± SD)	13.1 ± 4.9	15.6 ± 5.4	18.8 ± 6.6	< 0.001	14.4 ± 5.4	15.0 ± 5.4	18.0 ± 6.8	< 0.001
Saturated fats (g/day) (M ± SD)	26.8 ± 11.3	27.4 ± 10.6	30.9 ± 12.2	< 0.001	25.4 ± 10.9	27.2 ± 10.5	32.4 ± 12.0	< 0.001
Health measures								
Diabetes (% yes)	8.7	7.8	4.5	0.112	5.2	7.6	7.9	0.360
Stroke (% yes)	5.2	4.4	3.1	0.447	1.7	5.2	5.2	0.051
Cardiovascular disease (% yes)	25.0	23.8	24.1	0.942	23.1	23.1	25.9	0.668
Cholesterol, mmol/L (M ± SD)	5.4 ± 1.2	5.5 ± 1.1	5.6 ± 1.1	0.289	5.7 ± 1.1	5.5 ± 1.1	5.3 ± 1.2	< 0.001

Table 1. Continued

	HEALTH AWARE PATTERN			SWEET FOODS PATTERN		
	LOWER TERTILE	MIDDLE TERTILE	UPPER TERTILE	LOWER TERTILE	MIDDLE TERTILE	UPPER TERTILE
Demographic factors						
Age, years (M \pm SD)	69.5 \pm 0.8	69.5 \pm 0.8	69.5 \pm 0.8	69.5 \pm 0.8	69.5 \pm 0.9	69.4 \pm 0.8
Women (%)	32.6	52.2	71.3	47.7	55.5	53.6
Social class (%)						
1	21.1	18.3	15.6	15.1	21.7	18.4
2	35.9	40.5	40.6	36.6	38.1	41.7
3	18.3	23.9	29.9	21.8	24.9	25.3
3.5	22.2	13.8	11.0	20.8	13.9	12.5
4 + 5	2.5	3.5	2.8	5.6	1.4	2.1
SIMD score (M \pm SD)	5,039 \pm 5,872	5,056 \pm 5,886	5,762 \pm 9,834	5,091 \pm 8,165	5,106 \pm 5,874	5,631 \pm 8,047
Education, years (M \pm SD)	10.9 \pm 1.2	10.8 \pm 1.1	10.8 \pm 1.1	10.6 \pm 1.0	10.9 \pm 1.1	10.9 \pm 1.2
Age 11 IQ (M \pm SD)	102.5 \pm 13.1	100.5 \pm 14.7	101.4 \pm 14.0	100.2 \pm 12.9	102.2 \pm 14.2	102.0 \pm 14.6
MMSE score (M \pm SD)	28.9 \pm 1.2	29.0 \pm 1.2	29.0 \pm 1.2	28.7 \pm 1.4	29.1 \pm 1.1	29.1 \pm 1.1
Health behavior						
Alcohol, units/week (M \pm SD)	17.6 \pm 18.8	8.8 \pm 10.1	5.0 \pm 7.0	14.9 \pm 19.2	9.3 \pm 10.8	7.5 \pm 9.0
BMI (M \pm SD)	28.2 \pm 4.2	27.3 \pm 4.2	27.2 \pm 4.1	28.0 \pm 4.1	27.6 \pm 4.0	27.1 \pm 4.3
Physical activity, level (M \pm SD)	2.9 \pm 1.1	3.0 \pm 1.0	3.1 \pm 1.1	2.9 \pm 1.1	3.1 \pm 1.1	3.0 \pm 1.1
Smoking, pack years (M \pm SD)	31.1 \pm 28.0	29.2 \pm 27.4	17.0 \pm 18.1	30.0 \pm 30.1	25.3 \pm 24.4	22.1 \pm 20.9
Dietary factors						
Energy (kcal/day) (M \pm SD)	1,949 \pm 521	1,791 \pm 539	1,915 \pm 534	1,582 \pm 440	1,835 \pm 437	2,219 \pm 499
Sugars (g/day) (M \pm SD)	98.4 \pm 39.2	105.4 \pm 39.9	135.3 \pm 44.5	91.9 \pm 47.4	110.0 \pm 36.4	138.1 \pm 41.6
Vitamin C (g/day) (M \pm SD)	84.5 \pm 40.5	95.8 \pm 45.6	136.3 \pm 60.8	95.0 \pm 66.1	112.8 \pm 61.6	112.3 \pm 49.1
Fiber (g/day) (M \pm SD)	13.2 \pm 4.8	15.1 \pm 5.1	19.2 \pm 6.4	14.5 \pm 6.8	15.8 \pm 6.2	17.4 \pm 5.5
Saturated fats (g/day) (M \pm SD)	31.3 \pm 11.7	27.3 \pm 11.1	26.6 \pm 11.3	21.4 \pm 7.9	26.9 \pm 8.5	36.1 \pm 11.5
Health measures						
Diabetes (% yes)	7.2	6.9	7.3	10.0	5.5	5.8
Stroke (% yes)	4.8	3.8	4.1	4.1	5.5	3.1
Cardiovascular disease (% yes)	25.0	23.7	23.5	26.3	23.8	23.1
Cholesterol, mmol/L (M \pm SD)	5.5 \pm 1.1	5.5 \pm 1.2	5.5 \pm 1.1	5.5 \pm 1.2	5.5 \pm 1.1	5.5 \pm 1.2

Note: Analysis of variance was used to examine continuous variables and χ^2 -tests for categorical variables in relation to the differences between dietary pattern tertiles. p-values in bold indicate statistical significance.

Table 2. Associations between dietary patterns, age 11 IQ, and cognitive outcomes at age 70

DIETARY PATTERN	AGE 11 IQ M \pm SD	AGE 70 IQ M \pm SD	<i>g</i> FACTOR M \pm SD	PROCESSING SPEED M \pm SD	MEMORY M \pm SD	VERBAL ABILITY NART M \pm SD	VERBAL ABILITY WTAR M \pm SD
Mediterranean							
Lower tertile	98.5 \pm 13.0	99.4 \pm 13.1	-0.05 \pm 0.90	0.17 \pm 0.92	-0.07 \pm 0.91	33.0 \pm 7.3	39.9 \pm 6.5
Middle tertile	102.2 \pm 14.5	102.2 \pm 12.7	0.12 \pm 0.95	0.10 \pm 0.95	0.10 \pm 0.98	35.5 \pm 7.8	42.1 \pm 6.6
Upper tertile	103.5 \pm 14.0	103.7 \pm 12.4	0.28 \pm 0.97	0.18 \pm 0.91	0.18 \pm 0.98	37.1 \pm 7.5	43.4 \pm 6.1
p-value	<0.001	<0.001	<0.001	0.111	0.006	<0.001	<0.001
Traditional							
Lower tertile	106.4 \pm 12.4	105.4 \pm 10.7	0.45 \pm 0.86	0.30 \pm 0.86	0.39 \pm 0.89	38.6 \pm 6.6	44.4 \pm 5.2
Middle tertile	99.9 \pm 13.0	100.1 \pm 14.0	-0.06 \pm 0.94	0.006 \pm 0.95	-0.07 \pm 0.99	34.4 \pm 7.5	41.1 \pm 6.8
Upper tertile	98.2 \pm 15.0	100.2 \pm 12.9	-0.02 \pm 0.94	0.02 \pm 0.95	-0.10 \pm 0.94	32.8 \pm 7.8	40.0 \pm 6.6
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Health aware							
Lower tertile	102.5 \pm 13.1	103.2 \pm 12.0	0.18 \pm 0.92	0.11 \pm 0.95	0.09 \pm 0.93	35.0 \pm 7.8	41.7 \pm 6.6
Middle tertile	100.5 \pm 14.7	101.3 \pm 13.1	0.16 \pm 0.96	0.17 \pm 0.94	0.11 \pm 0.93	35.6 \pm 7.3	42.1 \pm 6.1
Upper tertile	101.3 \pm 14.0	101.0 \pm 13.4	0.23 \pm 0.95	0.04 \pm 0.89	0.02 \pm 1.0	35.1 \pm 8.0	41.6 \pm 6.9
p-value	0.213	0.081	0.104	0.279	0.543	0.572	0.659
Sweet foods							
Lower tertile	100.3 \pm 12.9	99.9 \pm 12.3	-0.01 \pm 0.9	0.06 \pm 0.9	-0.03 \pm 0.9	34.1 \pm 7.7	40.9 \pm 6.5
Middle tertile	102.0 \pm 14.5	102.6 \pm 13.4	0.18 \pm 1.0	0.11 \pm 0.9	0.10 \pm 1.0	35.6 \pm 7.8	42.0 \pm 6.7
Upper tertile	102.2 \pm 14.4	102.9 \pm 12.6	0.20 \pm 0.9	0.14 \pm 0.9	0.14 \pm 0.9	36.0 \pm 7.5	42.5 \pm 6.4
p-value	0.164	0.007	0.022	0.674	0.064	0.006	0.007

Notes: Each tertile X cognitive outcome has a reported mean and standard deviation.
 Analysis of variance was used to examine the relationship between dietary pattern tertiles and cognitive outcomes at age 70 and we report the p-value for trend.
 p-values in bold indicate statistical significance.

Table 3. General linear models showing associations between dietary patterns and cognitive outcomes at age 70

DIETARY PATTERN	MODEL	AGE 70 IQ*		g FACTOR		PROCESSING SPEED		MEMORY		VERBAL ABILITY NART		VERBAL ABILITY WTAR	
		p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2
Mediterranean	1	< 0.001 ^a	0.027	< 0.001 ^a	0.020	0.032 ^a	0.005	0.001 ^a	0.013	< 0.001 ^a	0.048	< 0.001 ^a	0.055
	2	0.088	0.003	0.330	0.001	0.519	0.001	0.392	0.001	0.002 ^a	0.011	< 0.001 ^a	0.017
	3	0.093	0.003	0.099	0.003	0.781	0.000	0.460	0.001	< 0.001 ^a	0.023	< 0.001 ^a	0.031
	4	0.767	0.000	0.960	0.000	0.205	0.002	0.870	0.000	0.024 ^a	0.006	0.001 ^a	0.013
Traditional	1	< 0.001 ^b	0.028	< 0.001 ^b	0.037	0.007 ^b	0.009	< 0.001 ^b	0.037	< 0.001 ^b	0.103	< 0.001 ^b	0.086
	2	0.026 ^b	0.006	0.002 ^b	0.011	0.671	0.000	< 0.001 ^b	0.019	< 0.001 ^b	0.056	< 0.001 ^b	0.045
	3	0.764	0.000	0.063	0.004	0.967	0.000	0.035 ^b	0.006	< 0.001 ^b	0.053	< 0.001 ^b	0.041
	4	0.473	0.001	0.507	0.001	0.285	0.001	0.079	0.004	< 0.001 ^b	0.035	< 0.001 ^b	0.027
Health aware	1	0.030 ^b	0.005	0.112	0.003	0.611	0.000	0.104	0.003	0.846	0.000	0.588	0.000
	2	0.053	0.004	0.177	0.002	0.492	0.001	0.186	0.002	0.916	0.000	0.800	0.000
	3	0.289	0.001	0.634	0.000	0.811	0.000	0.540	0.000	0.215	0.002	0.461	0.001
	4	0.235	0.002	0.542	0.000	0.813	0.000	0.520	0.001	0.325	0.001	0.568	0.000
Sweet foods	1	0.036 ^a	0.005	0.034 ^a	0.005	0.239	0.002	0.194	0.002	0.153	0.002	0.045 ^a	0.005
	2	0.359	0.001	0.281	0.001	0.721	0.000	0.569	0.000	0.809	0.000	0.358	0.001
	3	0.340	0.001	0.179	0.002	0.563	0.000	0.811	0.000	0.754	0.000	0.290	0.001
	4	0.647	0.000	0.377	0.001	0.760	0.000	0.922	0.000	0.855	0.000	0.544	0.000

Notes: * Age 70 IQ is already age-adjusted (age not included in the models for this outcome variable).

p-values in bold represent significant associations between dietary component and cognitive outcome.

Model 1: adjusted for sex and exact age at testing in later life; model 2: covariates as model 1 plus occupational social class; model 3: covariates as model 1 plus IQ at age 11 years from Moray House Test; and model 4: all covariates.

^apositive associations; ^bnegative associations.

sizes were reduced by 88% for NART (from $\eta_p^2 = 0.048$ in model 1 to $\eta_p^2 = 0.006$ in model 4), and 76% for WTAR (from $\eta_p^2 = 0.055$ in model 1 to $\eta_p^2 = 0.013$ in model 4).

Similarly, the negative associations between the “traditional” dietary pattern and cognitive abilities were diminished after adjustment of covariates, particularly age 11 IQ. For example, in the basic model 1, the “traditional” dietary pattern appears to explain 2.8% of the variance in age 70 IQ, 3.7% in general cognitive ability, and 3.7% in memory performance. However, after adjustment for age 11 IQ, these associations are reduced to 0%, 0.4%, and 0.6%, respectively. In the multivariable model that included age, sex, age 11 IQ, and occupational social class (model 4), the only statistically significant associations to remain were with the verbal ability measures. However, the effect sizes were again markedly attenuated from $\eta_p^2 = 0.103$ (model 1) to $\eta_p^2 = 0.035$ (model 4) for NART, and $\eta_p^2 = 0.086$ (model 1) to $\eta_p^2 = 0.027$ (model 4) for WTAR. In model 1, persons with higher scores on the “health aware” foods dietary pattern scored more poorly on a test of age 70 IQ, although the effect size was small ($\eta_p^2 = 0.005$). In model 1, persons with higher scores on the “sweet foods” pattern scored better on tests of age 70 IQ, general (*g*) factor, and WTAR. The effect sizes for these associations were small ($\eta_p^2 = 0.005$). After adjustment for age 11 IQ and SES, independently and in combination, there were no longer any significant associations between the “health aware” and “sweet foods” dietary patterns and cognitive domain scores at age 70.

We ran additional analyses using the fully adjusted model 4, which tested for an interaction effect between each dietary pattern and childhood IQ. We found that the associations between one of the dietary patterns, “health aware,” and cognitive outcomes differed depending on level of prior ability (data not shown). This interaction effect was present for the following cognitive outcomes: age 70 IQ ($p = 0.009$), memory ($p = 0.006$), and both verbal ability measures (NART $p < 0.001$, WTAR $p < 0.001$). Examination of the scatterplots representing these relationships, and the fit lines of the subgroups split at the median (low IQ/high IQ), showed that in those with a lower childhood IQ, there was some evidence of a relative detrimental effect of an increased “health aware” diet on these cognitive outcomes. For those with a higher childhood IQ there were either no or slightly positive effects. Therefore, childhood IQ moderated the effect of a “health aware” diet on cognition, but only on some of the outcomes. However, the differences in effect sizes (η_p^2) between the low- and high-IQ groups were small, e.g., 0.006 for age 70 IQ scores (0.009 and 0.003 respectively). We found no such

moderation effects of adult SES and dietary patterns on cognitive outcomes.

Discussion

In this study we examined associations between four empirically derived dietary patterns and important domains of cognitive function in a UK sample of men and women aged about 70 years. Before adjustment for childhood IQ and SES, our results suggested that following a “Mediterranean-style” diet was associated with better cognitive function, and following a “traditional” diet was associated with poorer cognitive function on all cognitive domains tested: IQ, general (*g*) cognitive ability factor, processing speed, memory, and verbal ability. This is consistent with some previous findings examining effects of diet on cognition in older age. We found, however, that current cognitive function was no longer associated with dietary patterns after adjustment for childhood IQ and adult SES. Only a small positive association persisted between the “Mediterranean-style” diet, and a small negative association between the “traditional” diet, and verbal ability. The relationship between the “health aware” dietary pattern and some of the cognitive measures (age 70 IQ, memory, and verbal ability) was moderated by childhood cognitive ability such that those with a lower childhood IQ consuming an increased “health aware” diet (characterized by a high consumption of fruit and low consumption of meats, eggs, spirits, and liqueurs) were at a relative disadvantage on these cognitive domains. The converse was true for those with a higher childhood IQ. However, the differences in effect sizes were small, and given that the “health aware” dietary pattern had little predictive value in the main analyses, these results may have limited clinical significance. Whereas there is a well-established link between a healthy, whole food diet, and a reduced risk of cognitive deficit, we found no evidence to suggest that this link is causal. Our hypothesis that the relationship between dietary patterns and cognition in old age might be confounded by childhood cognitive ability, and adult SES, was supported. This is, to our knowledge, the first study to examine the relationship between dietary patterns and cognition using a direct measure of cognitive ability obtained in youth to control for premorbid cognition. We used dietary patterns, derived using an *a posteriori* (data-driven) approach, to examine trends among food components from the overall diet rather than relying on a measure of adherence to a particular dietary pattern.

There has been much research attention focused on the effects of a healthy dietary pattern and reduced risk of chronic disease, particularly

coronary heart disease (CHD) (McCullough *et al.*, 2002; Hoffmann *et al.*, 2004; Drogan *et al.*, 2007; Liu *et al.*, 2009; Chiuve *et al.*, 2012) and diabetes (Fung *et al.*, 2007; DiBello *et al.*, 2008) as well as other outcomes such as mortality (Hamer *et al.*, 2010) and Alzheimer's disease (Scarmeas *et al.*, 2006a; 2006b; 2009a). Despite methodological differences between studies, dietary patterns characterized by a higher intake of fruit and vegetables, fish, and legumes and lower intake of red meats, processed foods, sweets, and saturated fats seem to be associated with the lowest risk of chronic disease (Gu and Scarmeas, 2011). However, studies investigating possible links between dietary patterns and cognitive changes associated with non-pathological aging are sparse. One line of investigation has focused solely on the health-promoting effects of the Mediterranean diet. It is characteristically rich in plant foods (fruit, vegetables, nuts, legumes, and cereals), wine, fish, and olive oil, and low in red meat and poultry. Adherence to this particular dietary pattern, measured using diet quality indices, has been widely reported to offer the best protection against cognitive aging in epidemiological studies (Féart *et al.*, 2009; 2010; Scarmeas *et al.*, 2009b; Tangney *et al.*, 2011). However, studying this dietary pattern in isolation is questionable, as the diets of certain populations, including the United Kingdom, may not closely resemble those of people living in Mediterranean countries.

In the three previous studies to date, which used a similar exploratory approach to determine distinct dietary patterns, there have been differences in derived dietary factors. Typically, two main factors emerge representing a "whole-food" or "healthy" dietary pattern, associated with better cognitive functioning, and a "processed-food" or "traditional" pattern, associated with poorer cognitive functioning (Akbaraly *et al.*, 2011; Kesse-Guyot *et al.*, 2012). Another study identified five dietary patterns using cluster analysis rather than PCA. Here the dietary pattern labeled as "healthy" was characterized by higher consumption of fish in men and fruit and vegetables in women, and was related to better cognitive performance (Samieri *et al.*, 2008). The current study found the two ubiquitous dietary patterns, namely "Mediterranean-style" and "traditional." The "traditional" pattern described in our study loaded highly on foods such as meat, pies, pasties and sausage rolls, mashed potatoes, tinned vegetables, and milk puddings, and represents a traditional (in Scotland) convenience diet. Two additional patterns, "health aware" and "sweet foods," accounted for a smaller percentage of the variance and were less predictive of cognitive outcomes. However, the four patterns identified in this study are not dissimilar to those found in other UK

populations, and the percentage of the variance in the diet explained by these factors is comparable (Hamer *et al.*, 2010).

Of these studies, the cognitive measures used have also varied from the MMSE only (Samieri *et al.*, 2008) to more comprehensive test batteries representing global cognitive function, verbal memory, and executive functioning (Kesse-Guyot *et al.*, 2012). Although their outcome was pathological aging, one further study paper (using a data-driven method) identified a dietary pattern similar to the "Mediterranean-style" pattern which was strongly protective of Alzheimer's disease risk (Gu *et al.*, 2010). Due to methodological differences in terms of the approaches used to quantify dietary patterns and the variations in cognitive endpoints measured, making comparisons between studies is problematic. That said, the present study supports and adds to the finding of Akbaraly *et al.* (2011) in that confounding plays a significant role in the relationship between dietary patterns and cognitive function to the extent that factors other than diet account for the majority of variance in the observed associations (Akbaraly *et al.*, 2011). In addition, in a recent paper by Shatenstein *et al.* (2012), although based on an *a priori* diet quality measure, a similar pattern of results emerged. The observed association between higher diet quality scores and better performance on the Modified Mini-Mental State examination disappeared after controlling for a set of potential confounders which included education (measured in years) and family income.

In our analysis, the dietary patterns–cognition relationship in old age could be accounted for, largely, by individual differences in prior ability (childhood IQ) and adult, occupation-based SES. This accords with the findings of some of our other studies where the same observation was made when alcohol consumption, (Corley *et al.*, 2011), BMI (Corley *et al.*, 2010b), and physical activity (Gow *et al.*, 2012a) were the health behaviors/lifestyle factors measured as putative determinants of differential cognitive aging. This is the only study to date to be able to directly control for prior ability in the dietary patterns–cognition relationship, using a well-validated measure taken in youth. Individual differences in cognitive function across the lifespan are highly stable, with correlations between 0.6 and 0.7 between age of 11 and 70–80 years (Deary *et al.*, 2000; 2004b; Gow *et al.*, 2011). Despite this, many studies designed to assess the extent of cognitive impairment in old age do not include data on early-life cognitive function, as it is rarely available. Traditionally, premorbid ability has been estimated via indirect sources such as education and tests of vocabulary and pronunciation. However, these proxy measures are somewhat

inadequate as they reflect life circumstances and knowledge; factors hypothesized to contribute to cognitive decline (Johnson *et al.*, 2011).

The current study lends further support to the possibilities of reverse causation or confounding, the former indicating that individuals with a higher childhood cognitive ability are more likely to adopt healthy eating patterns in later life and vice versa. This finding has been documented for several other health behaviors, including smoking (Kubicka *et al.*, 2001; Taylor *et al.*, 2003), alcohol consumption, physical activity (Batty and Deary, 2004; Anstey *et al.*, 2009) and diet (McNeill *et al.*, 2011). In the LBC1936 study, McNeill *et al.* (2011) reported some evidence of reverse causation in associations between vitamin C intake and NART, and verbal fluency; childhood IQ was found to cause marked attenuation. Higher lifetime trait IQ was also found to predict vitamin supplement use rather than supplement use predicting IQ in old age. Similarly, in the Danish Glostrup 1914 cohort, Gow *et al.* (2012b) reported that greater physical activity was no longer associated with less cognitive decline, after adjustment for baseline cognitive ability. They suggest that this indicates reverse causation or “preserved differentiation,” that is, more active individuals had a higher lifetime cognitive ability.

Although the current study is based on a healthy, non-pathological aging sample, it is plausible that the same mechanism may underlie the widely reported association between the Mediterranean diet and the risk of dementia or Alzheimer’s disease (see Allès *et al.*, 2012). Although there is a wealth of data to suggest that higher premorbid cognitive ability is protective of decline in later life (e.g., Bourne *et al.*, 2006; Gow *et al.*, 2011), the association with dementia risk is less consistent. Lower childhood intelligence was found to predict late- (but not early-) onset dementia (Whalley *et al.*, 2000). However, McGurn *et al.*, (2008) reported that it was a risk factor for vascular dementia but not Alzheimer’s disease. Some research suggests that the midlife diet may better predict dementia in late life as it reduces the impact of any recent changes to diet due to health status or cognitive impairment (i.e., reverse causation). Some studies have reported no association between risk of dementia in later life and dietary antioxidant intake at midlife in a male sample (Laurin *et al.*, 2004) and with midlife fruit and vegetable intake in males (Hughes *et al.*, 2010); however, there was a reduction in risk with increasing fruit and vegetable intake in women. A moderate intake of saturated fats in midlife was associated with an increase in risk of dementia and Alzheimer’s disease (Laitinen *et al.*, 2006). Although findings are often inconsistent, prospective studies are important for research on the etiology of cognitive aging;

dietary assessment at midlife and/or measures of long-term dietary intake likely reduce the possibility of confounding or reverse causation by factors caused by the disease process in later life. Whether the same pathways linking cognition and diet identified in the current study are relevant to dementia risk, requires further research from longitudinal studies.

There are several ways in which childhood IQ and SES could be related to dietary patterns. First, it could work via knowledge about nutrition (Wardle *et al.*, 2000). People with lower cognitive ability may be less likely to acquire the concepts and knowledge to ensure a healthy diet and make favorable food choices. The 1970 British Cohort Study (BCS70) found that those with a higher childhood mental ability score reported a significantly higher intake of fruit, vegetables, wholemeal bread, poultry, fish, and foods fried in vegetable oil in adulthood, and a lower intake of chips, non-wholemeal bread, cakes, and biscuits in adulthood (Batty *et al.*, 2007). The second way in which childhood IQ and SES could be linked to dietary patterns is via financial circumstances. Higher cognitive ability scores in childhood predict advantageous social circumstances in adulthood, including job and financial attainment and a higher SES (Deary *et al.*, 2005). Diet quality follows a socioeconomic gradient (Hare-Bruun *et al.*, 2011); lower quality diets (consisting of cheaper foods with a lower nutritional value) are more likely to be consumed by those with lower education/SES and more limited economic means. Third, it might come about via self-management of health. IQ may affect how people interpret and respond to health advice (Taylor *et al.*, 2003). IQ is associated with levels of health literacy, a crucial factor in health management (Murray *et al.*, 2011). Essentially, cognition may influence the extent to which people manage their own risk for cognitive decline. Anstey *et al.* (2009) proposed an interactive cycle involving cognition, self-management of health (including diet), and ultimate cognitive outcomes. The current study supports this possible mechanism.

Therefore, controlling for childhood cognitive ability is advantageous in order to properly test whether there is any variance in cognitive function in old age explained by diet over and above that explained by an individual’s prior ability. Some associations were found between higher “Mediterranean-style” pattern scores and better verbal ability, but only on one of the tests, and higher “traditional” pattern scores and poorer verbal ability, although both were markedly attenuated after adjustment. This may be a true finding. However, it is possible that some associations persist between dietary patterns and verbal ability because verbal ability tests, such as the NART and WTAR, reflect

one's peak level of cognitive ability in adulthood. Such tests are purported to reflect one's crystallized intelligence, which is related to education and intellectual, social, and cultural development across the lifespan, not necessarily captured by tests such as the MHT. Compared with the skills measured by traditional IQ-type tests, verbal ability is relatively unaffected by non-pathological (Carroll, 1993; Schaie, 1996) and pathological age-related changes (McGurn *et al.*, 2004). In addition, peak adult cognitive ability is likely to be associated with lifestyle preferences that influence the adoption of health behaviors, including diet, supporting the concept of reverse causation. Furthermore, the proportion of the total variance in verbal ability scores explained by these dietary patterns was between 0.6% and 1.30% for the "Mediterranean-style," and approximately 3.0% for the "traditional" dietary pattern. These effect sizes are small. However, around 50% of the variance in cognitive abilities in old age is explained by childhood IQ. It is likely that a large number of lifestyle/behavioral predictors will have small effects, so it is inevitable that the effect sizes of other variables will be relatively small. These effect sizes are comparable to those consistently cited behaviors linked with cognitive aging – smoking and physical activity (as well as apolipoprotein E (APOE)) – which account for 1–2% of the variance. It is important to know the effects of lifestyle predictors, such as diet, so that we can discover the combination of factors that might help people age better.

Strengths and limitations

In contrast with the conventional approach, which focuses on a single nutrient or a few nutrients or foods in isolation, identifying dietary patterns takes into account overall eating patterns. The current study has the advantage of using a data-driven approach to determine dietary patterns, independent of previous hypotheses, to explore the factors that account for correlations among reported food components in the overall diet. On the other hand, the *a priori* method of measuring diet quality makes assumptions about what constitutes a healthy diet based on current theory regarding nutrition (Allès *et al.*, 2012). Further strengths of this study include the large sample size, narrow age cohort (minimizing age and cohort effects), and data collection using a well-validated questionnaire and comprehensive cognitive (and covariate) measures. Most notably, we have a repeated measure of cognitive abilities at two distinct time-points across the lifespan (age 11 and 70 years). A direct measure of prior cognitive ability is rarely available. An advantage of using a measure of IQ obtained in youth

is the lower prevalence of known conditions which might impact on IQ/cognition such as hypertension (Manolio *et al.*, 2003) and diabetes (Awad *et al.*, 2004).

Inevitably, there were also some limitations. We used a single measure of diet (FFQ) designed to capture dietary habits in the short term, but not necessarily representative of dietary habits over a longer period of time. Although a potential limitation, the FFQ (Masson *et al.*, 2003) has good repeatability (dietary intake in later life is reasonably stable in the short term) and good validity for most nutrients in community-dwelling older populations (Jia *et al.*, 2008; McNeill *et al.*, 2009). The four extracted dietary components explain less than 12% of the variance. Hence, it could be argued that major dietary effects on cognition could occur in the remaining 88% of the shared variance, or that specific food types might be associated with higher cognitive scores. A further potential limitation relates to the influence of age-related cognitive decline on dietary choices, e.g., the adoption of more convenience foods as represented by the "traditional" dietary pattern. Reverse causation of this kind may distort the observed associations. That said, we excluded persons based on the MMSE score, and therefore we were confident that the current samples were free from cognitive impairment. Furthermore, the LBC1936 study is a self-selecting sample. Compared with the general population, it is likely to be healthier and more cognitively able. Of course, given our interests in the lifelong association between dietary patterns and cognitive abilities, it would have been useful to have information on dietary patterns from childhood, and more information on both diet and cognition from points in the life course between the age of 11 and 70 years.

Conclusions

Dietary patterns are a promising strategy for analyzing the associations between food and cognitive performance in epidemiological investigations. However, our findings urge caution in interpreting diet–cognition associations as causal effects in that direction. Our results suggest a pattern of reverse causation (or confounding); a higher childhood cognitive ability (and adult SES) might predict choice of and/or adherence to a "healthy" dietary pattern and better cognitive performance in old age. Our models show no direct link between diet and cognitive performance in older age; instead, they raise the possibility that they are related via the lifelong stable trait of intelligence.

Conflict of interest

None.

Description of authors' roles

J. Corley was involved in data collection, performed the statistical analyses, and led the writing of the paper. J. M. Starr and I. J. Deary contributed to study design, interpretation of analyses, and drafting of the manuscript. G. McNeill contributed to the interpretation of analyses and drafting of the manuscript.

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Serum cholesterol and cognitive functions: the Lothian Birth Cohort 1936

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ABSTRACT

Background: We examined the associations between serum cholesterol measures, statin use, and cognitive function measured in childhood and in old age. The possibility that lifelong (trait) cognitive ability accounts for any cross-sectional associations between cholesterol and cognitive performance in older age, seen in observational studies, has not been tested to date.

Methods: Participants were 1,043 men and women from the Lothian Birth Cohort 1936 Study, most of whom had participated in a nationwide IQ-type test in childhood (Scottish Mental Survey of 1947), and were followed up at about age 70 years. Serum cholesterol measures included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, and cholesterol:HDL cholesterol ratio. Cognitive outcome measures were age 70 IQ (using the same test as at age 11 years), general cognitive ability (*g*), processing speed, memory, and verbal ability.

Results: Higher TC, higher HDL-C, and lower triglycerides were associated with higher age 70 cognitive scores in most cognitive domains. These relationships were no longer significant after covarying for childhood IQ, with the exception a markedly attenuated association between TC and processing speed, and triglycerides and age 70 IQ. In the fully adjusted model, all conventionally significant ($p < 0.05$) effects were removed. Childhood IQ predicted statin use in old age. Statin users had lower *g*, processing speed, and verbal ability scores at age 70 years after covarying for childhood IQ, but significance was lost after adjusting for TC levels.

Conclusions: These results suggest that serum cholesterol and cognitive function are associated in older age via the lifelong stable trait of intelligence. Potential mechanisms, including lifestyle factors, are discussed.

Key words: cholesterol, cognitive function, childhood IQ, aging

Introduction

It is widely reported that some cognitive abilities show a mean decline with age. However, there is variability in the magnitude and rate of decline among older individuals. Here, we test the suggestion that people's differences in serum lipids and statin medication might contribute to differences in cognitive functions in older age.

Serum lipoprotein levels have been identified as a potential modifiable risk factor for cognitive impairment (Kivipelto and Solomon, 2006). Numerous studies suggest that high midlife serum total cholesterol (TC) levels are associated with greater late-life cognitive impairment (Whitmer

et al., 2005; Solomon *et al.*, 2007; Anstey *et al.*, 2008; Beydoun *et al.*, 2010; Reynolds *et al.*, 2010). An increased risk of cardiovascular pathologies with a higher midlife TC (Simons *et al.*, 2001; Berry *et al.*, 2008) may, in part, explain the later risk of cognitive impairment. However, the association between late-life TC levels and cognitive function remains unclear. With age, there is typically a drop in cholesterol (Abbott *et al.*, 1997) and high-density lipoprotein cholesterol (HDL-C) levels (Formiga *et al.*, 2012), as cholesterol synthesis and absorption decrease (Tilvis *et al.*, 2011). A 2009 review (van Vliet *et al.*, 2009) of cross-sectional and longitudinal studies concluded that there is either no association in healthy older people (Li *et al.*, 2005; Reitz *et al.*, 2005) or a decreased risk of cognitive impairment with high late-life TC levels (e.g. Mielke *et al.*, 2005; see also Piguet *et al.*, 2003; Karlamangla *et al.*, 2004; Panza *et al.*, 2009). Moreover, findings suggest the relation between high TC levels and cardiovascular risk in late-life (over age 70 years) is weak, at best

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(Simons *et al.*, 2001; van Vliet *et al.*, 2009). The decreased risk might specifically apply to certain cognitive domains, e.g. attention and word fluency tasks (Elias *et al.*, 2005). In contrast to these findings, TC correlated negatively with brain gray matter volume in a sample of men and women in their late 70s, supporting the role of elevated serum cholesterol in brain shrinkage and age-related neurodegeneration (Whalley *et al.*, 2003).

High-density lipoprotein cholesterol offers some protection against cardiovascular disease (CVD) in both midlife and late-life (de Freitas *et al.*, 2011) but there is no conclusive evidence that “protection” from HDL-C extends to cognitive function at either life stage. Cross-sectional studies were more likely to show an association between high HDL-C and better cognitive performance in old age (Atzmon *et al.*, 2002; Reitz *et al.*, 2010; van Exel *et al.*, 2002). In general, the results of longitudinal investigations have been unable to support the high HDL-C-better cognitive function association in those over the age of 65 years (Henderson *et al.*, 2003; Reitz *et al.*, 2005, Reitz *et al.*, 2008). However, many of the reported studies have been restricted to brief tests of global cognition (Atzmon *et al.*, 2002; Yaffe *et al.*, 2002; Solomon *et al.*, 2009; Formiga *et al.*, 2012).

Statins are the first-line treatment option for hypercholesterolemia; by reducing serum cholesterol levels, statins lower the risk of angina, heart attack, and stroke. Whether or not statins can improve cognitive function in older age is unclear. Statins were reported to have beneficial effects on cognitive outcomes in several clinical trials (Parale *et al.*, 2006; Carlsson *et al.*, 2008), but no association in others (Trompet *et al.*, 2010), even though statin treatment successfully reduced the risk of cardiovascular disease in the same sample (Shepherd *et al.*, 2002). Population-based studies suggest a potential role for statins in preventing cognitive decline (Yaffe *et al.*, 2002; Starr *et al.*, 2004; Bernick *et al.*, 2005; Solomon *et al.*, 2009).

Other possible confounding factors in the lipid-cognition association should be considered. Given that childhood cognitive ability is the most important determinant of adult cognitive ability (accounting for around half the variance; Deary *et al.*, 2000) and a predictor of a healthy diet and lifestyle in adulthood (Batty and Deary, 2004; Batty *et al.*, 2007), and morbidity and mortality rates (Deary *et al.*, 2010; Kilgour *et al.*, 2010), the direction of causation is a prime concern. Cross-sectional relationships may reflect the observed association between a higher “trait” IQ and healthy behaviors in adulthood which are conducive to a “desirable” lipid profile, low CVD risk, and other favorable health outcomes. There is much evidence to suggest that it is unsaturated fatty acids, typical

of a Mediterranean-type diet that have some benefit on serum lipid profiles (Siri-Tarino *et al.*, 2010) and cognition (Coscina *et al.*, 1986; Whalley *et al.*, 2004) in comparison to a low-fat or high-saturated-fat diet. Therefore, early-life cognitive ability and, by association, socioeconomic status (SES; Sacker *et al.*, 2002; Hagger-Johnson *et al.*, 2012), may be important confounders of the cholesterol-cognition relationship in later-life.

The present study attempts to address gaps in the knowledge of the cholesterol-statins-cognition associations by examining generally healthy, older people without dementia from Lothian Birth Cohort 1936 (LBC1936) Study and their functioning over several major aging-relevant cognitive domains. They are unusual in being an older-age cohort for whom there are valid cognitive ability test scores from age 11 years. Our goals were to determine: (1) the nature of the associations between serum cholesterol measures and cognitive function at age 70 years; (2) the amount of variance in cognitive performance explained by cholesterol levels once we have accounted for the contribution of prior cognitive ability measured in childhood (age 11 years); (3) whether additional statistical control for potential covariates further attenuate the lipids-cognition associations; (4) the relationship between statin use and life-long cognitive ability (at ages 11 and 70 years).

Methods

Study sample

The Lothian Birth Cohort 1936 (LBC1936) comprises 1,091 men and women, almost all of whom were resident in Edinburgh and the surrounding Lothian region at about age 70 years. Early life (mean age 11 years) intelligence test scores are available for most in this sample, because they are surviving participants of the Scottish Mental Survey of 1947 (SMS1947; Deary *et al.*, 2009). On June 4th 1947, about 95% of school children born in 1936 and attending Scottish schools ($n = 70,805$), took a version of the Moray House Test (MHT) No.12 (Scottish Council for Research in Education – SCRE, 1933; 1949). The MHT is a group-administered test of general intelligence. This test was concurrently validated against the Terman-Merill revision of the Binet scales with a correlation of about 0.8 (SCRE, 1949). Scottish Council for Research in Education recorded and archived these scores and made them available to the LBC1936 Study. Participants in Edinburgh and the surrounding areas were traced in later life and invited to take part in a longitudinal study of cognitive aging, hereafter referred to as

the LBC1936 Study. Full recruitment and testing procedures are reported in a free-access protocol paper (Deary *et al.*, 2007). In brief, the assessment involved detailed cognitive, medical, and other testing, and self-completed questionnaires, and took place between 2004 and 2007 when participants were aged about 70 years.

Of the 1,091 participants in the study, 37 had missing cholesterol data. Of the remaining participants, 11 scored less than 24 on the Mini-Mental State Examination; this cut-off is often used to indicate possible dementia. These participants were excluded from the analyses. The sample *n* for the current study is 1,043 (50.1% men).

Ethics permission for the Lothian Birth Cohort 1936 (LBC1936) study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee for Scotland (LREC/2003/2/29). The research was carried out in compliance with the Helsinki Declaration. All participants gave their written, informed consent.

Measurement of cholesterol

Serum cholesterol was measured as part of a blood analysis profile. Non-fasting blood was drawn on the day of cognitive assessment and analyzed within 24 h in serum stored at 4 °C using an enzymatic Quinoneimine dye method measuring at 500 nm, at the Western General Hospital, Edinburgh. Lipids are expressed in mmol/L. The main analyses were conducted using cholesterol measures as continuous variables. For illustrative purposes only, each lipid measure was also classified into three clinically relevant categories, in accordance with the National Cholesterol Education Program (Adult Treatment Panel III, 2001). Total cholesterol (TC) groups were: <5.2 mmol/L (low), 5.2 to 6.2 mmol/L (intermediate), >6.2 mmol/L (high). The range of TC in the current sample was 2.7 to 10.8 mmol/L (mean = 5.5, SD = 1.2). High-density lipoprotein cholesterol groups were: <1.3 mmol/L (low), 1.3 to 1.5 mmol/L (intermediate), >1.5 mmol/L (high). The range of HDL-C in the current sample was 0.53 to 3.82 mmol/L (mean = 1.5, SD = 0.44). Triglycerides groups were: <1.7 mmol/L (low), 1.7 to 2.2 mmol/L (intermediate), >2.2 mmol/L (high). The range of triglycerides for the current sample was 0.47 to 16.32 mmol/L (mean = 1.6, SD = 0.91). The ratio of TC to HDL cholesterol (chol:HDL-C) provides a stronger prediction of coronary heart disease (CHD) risk (Ingelsson *et al.*, 2007) and CHD mortality (Prospective Studies Collaboration, 2007) because these components are related to risk in opposite directions. A lower ratio is clinically more desirable in terms of CHD risk. Chol:HDL-

C ratio groups were: <3.5mmol/L (low); 3.5 to 5.1mmol/L (intermediate); >5.1mmol/L (high) (range 0.38 to 9.50, mean = 3.76, SD = 1.07). Low-density lipoprotein (LDL) cholesterol measurement was not available in this sample. For the purposes of this study, cholesterol classification groups are hereafter referred to as low, intermediate, and high.

Cognitive functions

The cognitive test battery was chosen to provide a comprehensive assessment of cognitive function. Full details of the cognitive tests have been provided elsewhere (Deary *et al.*, 2007). Participants took six subtests from the Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III; Wechsler, 1998a), namely: Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; Symbol Search. Participants took subtests from the Wechsler Memory Scale-III^{UK} (WMS-III; Wechsler, 1998b), namely: Logical Memory; Spatial Span; Verbal Paired Associates. Participants also completed a simple and choice reaction time task (Cox *et al.*, 1993; Deary *et al.*, 2001) and a computer-based visual processing speed task known as Inspection Time (Deary *et al.*, 2004).

From these tests, composite cognitive function scores were formed to represent three cognitive domains (general cognitive ability, processing speed, and memory). The previous extraction of these scores, using principal components analysis, has been described in detail elsewhere (Luciano *et al.*, 2009; Corley *et al.*, 2010). A general cognitive ability factor (often referred to as *g*), was derived from scores on the WAIS-III subtests: Letter-Number Sequencing; Matrix Reasoning; Block Design; Digit Symbol; Digit Span Backwards; Symbol Search. A processing speed factor was derived from scores on a set of mental processing speed measures, namely: Symbol Search; Digit Symbol; Simple and Choice Reaction Time mean; Inspection Time. A memory factor was derived from scores on a set of memory measures, namely: Logical Memory I (immediate) and II (delayed) recall; Spatial Span Forwards and Spatial Span Backwards; Verbal Paired Associates I (immediate) recall and II (delayed) recall; Letter-Number Sequencing; Digit Span Backwards.

Participants re-sat the MHT at age 70 years. Moray House Test scores at ages 11 and 70 years were corrected for age in days at time of testing and converted into IQ-type scores for the sample (*M* = 100, *SD* = 15).

Verbal ability was assessed using the National Adult Reading Test (NART; Nelson and Willison, 1991) which is widely used to estimate prior

cognitive ability; it requires the pronunciation of a list of 50 irregular words. The Mini-Mental State Examination (MMSE), a standardized brief screening measure for cognitive pathology (Folstein *et al.*, 1975), was used as a brief screening test for dementia. Scores range from 0 to 30, with a score of less than 24 often used to indicate possible dementia.

Covariates

Participants provided general demographic information including age, years of full-time education, and social class. Adult occupational social class was derived from each participant's highest reported occupation (for women, their spouses occupation was used if higher than their own) and classified into one of six categories ranging from I (professional occupations) to V (unskilled occupations), with III divided into IIIN (non-manual) and IIIM (manual) using the UK Registrar General's Classification of Occupations, 1980 (Office of Population Censuses and Surveys, 1980). For analyses, occupational social classes IV and V were combined due to the small number of participants ($n = 4$) in class V. The number of years of full-time education, self-reported history of hypertension, stroke, CVD, high cholesterol, and statin use were recorded ("yes/no") by an interviewer at the time of assessment. Dietary intake and alcohol use were recorded using the Scottish Collaborative Group Food Frequency Questionnaire (SCG-FFQ) version 7.0 (Jia *et al.*, 2008). Alcohol use was expressed as units of alcohol consumed in a typical week. Dietary intake of saturated fats (grams per day), polyunsaturated fatty acids (PUFAs, grams per day), and cholesterol (milligrams per day) were calculated based on responses to the 168-item FFQ. Level of physical activity was obtained from a self-report questionnaire. This measure was coded as follows: 1 – "household chores;" 2 – "walking etc. 1–2 times a week;" 3 – "walking etc. several times a week;" 4 – "exercise 1–2 times a week;" 5 – "exercise several times a week;" 6 – "keep-fit/heavy exercise/sport several times a week." Height and weight were measured as part of a physical examination. Body mass index (BMI) was calculated as weight (kg) divided by height squared (in square meters). Adiposity is an important influence in adult lipid profiles; BMI is often used as a proxy measure of adiposity and, in adults, BMI is positively related to TC and negatively related to HDL-C (Folsom *et al.*, 1994).

Statistical analysis

Analyses were performed using IBM SPSS, version 19 (IBM, NY, USA). Demographic and health

differences between clinically relevant cholesterol categories were demonstrated using analysis of variance (ANOVA) and χ^2 tests, as appropriate. We used linear regression to examine the relationship between each lipid measure's three-level grouping (for TC, HDL-C, triglycerides, and chol:HDL-C) and cognitive outcomes (general (g) cognitive ability, processing speed, memory, and verbal ability (NART) and age 70 MHT-IQ) and between statin use and cognitive function in youth and old age. Additional logistic regression models were used to examine the relationship between age 11 IQ (divided into quartiles) and statin use. We report odds ratios and 95% CI.

In the main analyses, multiple linear regression models were used to test the association between the continuous distributions of lipid measures with each cognitive performance measure. Three models were fit to the data. Model 1 included exact age at testing (in days) and sex. In model 2, age 11 IQ was added. In model 3, we further included occupational social class, statin use and history of CVD. All effects are reported using standardized regression coefficients, also known as "betas." These coefficients are calculated from standardized data and reflect the impact on the outcome variable of a change of one standard deviation in the predictor variables. p -values are reported. The 0.05 level of significance was used for all data analyses.

Results

Participant characteristics

In Table 1, demographic and covariate data are displayed by TC group, based on TC clinical categories. The mean TC values ($M \pm SD$) for each TC group were: (1) 4.4 ± 0.53 ; (2) 5.7 ± 0.32 ; (3) 7.0 ± 0.64 . There were notable differences in several characteristics in relation to TC levels. Higher TC levels were associated with being younger, being female, being in a more "professional" social class, having a lower BMI, smoking less, having a sedentary lifestyle, and having a lower prevalence of CVD, hypertension, stroke and high cholesterol, and with less reported statin use. All of these are factors associated with a healthy lifestyle. In terms of dietary intake, a higher TC level was associated with a lower score on the conventional dietary pattern (which loads highly on saturated fats and convenience foods), lower saturated fats and a lower dietary cholesterol intake. In contrast, a higher TC level was associated (rather counter-intuitively) with lower dietary PUFAs, which are generally considered to have a beneficial effect on health and HDL cholesterol while reducing LDL cholesterol. The

Table 1. Characteristics of participants according to serum total cholesterol (TC) group at age 70 years

CHARACTERISTICS	n	LOW TC <5.2 mmol/L (n = 435)	INTERMEDIATE TC <5.2–6.2 mmol/L (n = 355)	HIGH TC >6.2 mmol/L (n = 253)	p
		MEAN ± SD	MEAN ± SD	MEAN ± SD	
Age (years)	1,043	69.7 ± 0.80	69.5 ± 0.84	69.3 ± 0.82	<0.001
Education§ (years)	1,043	10.7 ± 1.1	10.8 ± 1.1	10.7 ± 1.1	0.157
MMSE	1,042	28.8 ± 1.3	29.0 ± 1.2	28.9 ± 1.3	0.030
Age 11 IQ (MHT)	987	98.3 ± 16.0	100.7 ± 15.1	100.6 ± 12.0	0.001
BMI (kg/m ²)	1,042	28.4 ± 4.5	27.6 ± 4.5	26.9 ± 3.6	<0.001
Alcohol (units/week)	1,043	10.9 ± 16.0	10.5 ± 12.1	9.9 ± 12.7	0.682
Saturated fats (g/day)	896	28.5 ± 12.3	31.0 ± 15.3	26.6 ± 11.3	0.001
PUFAs (g/day)	896	11.9 ± 5.4	11.8 ± 5.6	10.3 ± 4.3	0.001
Dietary cholesterol (mg/day)	896	281.8 ± 118.5	295.6 ± 139.7	259.3 ± 93.1	0.003
Mediterranean diet score	851	−0.10 ± 0.83	0.11 ± 1.2	0.03 ± 1.0	0.025
Conventional diet score	851	0.10 ± 1.0	−0.01 ± 1.0	−0.17 ± 1.0	0.006
	n	No. (%)	No. (%)	No. (%)	
Sex, men	1,043	275 (63.2)	171 (48.2)	77 (30.4)	<0.001
Social class‡	1,023				<0.001
I	186	61 (14.0)	74 (20.8)	51 (20.2)	
II	383	157 (36.1)	121 (34.1)	105 (41.5)	
III Non-manual	233	88 (20.2)	79 (21.4)	66 (26.1)	
III Manual	181	98 (22.5)	59 (16.6)	24 (9.5)	
IV and V	40	21 (4.8)	14 (3.9)	5 (2.0)	
Physical activity (1 and 2)	928	128 (33.7)	74 (23.4)	52 (22.4)	0.002
Current smokers	1,043	62 (14.2)	44 (12.4)	31 (12.2)	0.007
With CVD	1,043	174 (40.0)	58 (16.3)	28 (11.1)	<0.001
With hypertension	1,043	236 (54.3)	105 (29.6)	71 (28.1)	<0.001
With stroke	1,043	44 (49.7)	2 (0.6)	5 (2.0)	<0.001
With high cholesterol	1,043	216 (49.7)	79 (22.2)	73 (28.9)	<0.001
Using statins	1,043	234 (53.8)	38 (10.7)	9 (3.6)	<0.001

TC = total cholesterol; MMSE = Mini-Mental State Examination; MHT = Moray House Test; BMI = body mass index; PUFAs = polyunsaturated fatty acids; CVD = cardiovascular disease; SD = standard deviation.

§Education was coded as number of years in full-time education.

‡Occupational social class was measured on a scale of I to V in which I represented executive/professional occupations and V represented unskilled labor.

Physical activity was measured on a scale from 1 to 6 in which 1 represented the least physical activity. Results for groups 1 and 2 combined (representing the most sedentary groups) versus groups 3 to 6 are presented.

p-values are from ANOVA for continuous variables and χ^2 tests for categorical variables. Probabilities for significant effects are given in boldface; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

intermediate group had the highest MMSE and age 11 IQ score, in addition to the highest intake of saturated fats, dietary cholesterol, and the highest Mediterranean diet score (which loads highly on vegetables, fish, beans, and pulses). There was no significant difference in education level or alcohol consumption between the three groups.

Post hoc tests using the Bonferroni correction revealed that the statistical differences in age, social class, BMI, physical activity level, and prevalence of disease (as above) existed between the low TC group versus the other two groups (corrected $p < 0.05$; data not shown). For these variables there were no statistical differences between the intermediate- and high-TC groups. In the low-TC group, there was a markedly increased prevalence of CVD (40%), stroke (50%), and hypertension (54%) compared with the highest TC group (11%,

2%, and 28% respectively). Lower age 11 IQ and more pack years of smoking were found in the low-TC group compared to the high-TC group only ($p = 0.001$) and MMSE score differed between the low and intermediate groups only ($p = 0.029$). There were statistical differences in gender between all TC groups ($p < 0.001$). Dietary intake of saturated fats and cholesterol differed between the intermediate and high groups only and PUFAs differed between intermediate and high, and also between low- and high-TC groups.

Associations between childhood IQ, age 70 IQ, and other cognitive function at age 70 years

The Pearson correlation between MHT-derived IQ at age 11 years and IQ at age 70 years was 0.69 ($p < 0.001$). Age 11 IQ was also strongly correlated

with all other cognitive outcomes; general cognitive ability ($r = 0.61$, $p < 0.001$); speed ($r = 0.46$, $p < 0.001$); memory ($r = 0.54$, $p < 0.001$); NART ($r = 0.69$, $p < 0.001$).

Associations between serum cholesterol groups and cognitive function at age 70 years

Table 2 presents the results of unadjusted linear regression analyses with serum cholesterol groups as the (categorical) predictor variables and cognitive outcomes as the dependent variables. Higher TC predicted better performance on tests of general cognitive (g) ability, processing speed, memory, and verbal ability, but not age 70 IQ. *Post hoc* multiple comparison tests revealed that the significant differences were between groups 1*2 and 1*3 and not between 2*3.

Higher HDL-C predicted better cognitive scores on all cognitive domains measured, including age 70 IQ. For the three composite cognitive factors (g , speed, memory), *post hoc* tests revealed that the significant differences were between groups 1*2 and 1*3 and not between 2*3, as found for TC. However, for verbal ability and age 70 IQ, the significant differences were between groups 1*3 and 2*3 but not 1*2. Those in the high HDL-C group had a higher average age 70 IQ by 4.5 points, than those in the “low” HDL-C group.

Higher triglycerides predicted worse performance on tests of age 70 IQ (for all group contrasts) and verbal ability (groups 1*2, 1*3) but not for the composite cognitive factors. Although non-significant, a negative trend of lower cognitive scores for g , speed, and memory with higher triglycerides was observed. Compared with a high triglycerides group, a low (clinically more desirable) level of triglycerides was associated with a higher average age 70 IQ by 5.9 points and a higher verbal ability.

A significant inverse association was found between chol:HDL-C ratio groups and memory scores such that those with a lower (more desirable) ratio was associated with better scores, but this difference was significant only between groups 1*3. This inverse trend was apparent with the other cognitive scores but these differences were not statistically significant.

Significant associations were found between childhood IQ and three of the four cholesterol measures (TC, HDL-C, triglycerides, overall $p = 0.001$). Childhood IQ was significantly associated with TC (groups 1*3) and HDL-C (1*2, 1*3) in a positive direction, and with triglycerides (1*3) in a negative direction. Differences in childhood IQ points between the low- and high-cholesterol groups were as follows: TC 4.4 IQ points; HDL-C 6.1 IQ points; triglycerides 5.5 points.

Associations between childhood IQ and covariates

Age 11 IQ was significantly and negatively associated with occupational social class (standardized $\beta = -0.393$, $p < 0.001$), such that individuals with a higher age 11 IQ were more likely to belong to a more professional social class (classes 1 and 2), and with CVD history ($\beta = -0.077$, $p < 0.015$), such that individuals with a higher age 11 IQ were less likely to have a history of CVD.

Associations between statin use and cognitive function at ages 11 and 70 years

First, we examined whether there was an association between age 11 IQ (as a predictor) and statin medication use in later life. Table 3 shows a significantly higher prevalence of statin use in adulthood in those who had a lower age 11 IQ score (standardized $\beta = -0.077$, $p = 0.015$). Using a logistic regression model (data not presented) where the predictor variable was age 11 IQ (divided into quartiles) and the outcome variable was statin use, we found that compared to those in the highest age 11 IQ quartile (fourth quartile; reference group) those in the lowest age 11 IQ quartile had 1.6 times higher odds (95% CI = 1.05–2.32), and those in the second quartile had 1.4 times higher odds (95% CI = 0.94–2.03), and those in the third quartile had 1.2 times higher odds (95% CI = 0.79–1.78) of taking statin drugs in later life.

Second, we examined whether there was an association between statin use (as a predictor) and cognitive function assessed at age 70 years. We found that statin use predicted poorer performance on the same test of IQ repeated almost 60 years later ($p = 0.024$). The difference in terms of IQ points is small, but the relationship is significant and linear. Statin use was associated with significantly lower cognitive performance across all other cognitive domains tested, compared with non-statin use. In order to account for the effect of lifelong cognitive ability on these associations we included age 11 IQ as a covariate. Associations remained, though with marked attenuation of the effect sizes, for g , processing speed and verbal ability, but not memory or age 70 IQ. However, when TC was added to this model to adjust for blood cholesterol levels, there were no longer any significant relationships between statin use and cognition.

Adjusted associations between serum cholesterol measures (as continuous variables) and cognitive function at age 70 years

Table 4 shows the results of multiple linear regression models used to examine the association

Table 2. Cognitive function scores at age 70 years in relation to clinical categories (low, intermediate, and high) of TC, HDL-C, triglycerides, and Chol:HDL-C ratio

LIPID LEVELS		GENERAL (g) ABILITY			PROCESSING SPEED			MEMORY			VERBAL ABILITY – NART			AGE 70 IQ			AGE 11 IQ		
		MEAN ± SD		GROUP CONTRASTS	MEAN ± SD		GROUP CONTRASTS	MEAN ± SD		GROUP CONTRASTS	MEAN ± SD		GROUP CONTRASTS	MEAN ± SD		GROUP CONTRASTS	MEAN ± SD		GROUP CONTRASTS
n				p-VALUE			p-VALUE			p-VALUE			p-VALUE			p-VALUE			p-VALUE
<hr/>																			
TC		1,043																	
1	435	-0.09 ± 0.99	1*2 0.008	-0.13 ± 1.02	1*2 0.001	-0.08 ± 1.01	1*2 0.012	33.8 ± 8.4	1*2 0.042	99.7 ± 14.8	1*2 0.158	98.3 ± 16.0	1*2 0.092						
2	355	0.09 ± 0.99	1*3 0.009	0.11 ± 0.93	1*3 0.001	0.10 ± 0.95	1*3 0.031	34.9 ± 8.2	1*3 0.004	101.1 ± 14.2	1*3 0.260	100.7 ± 15.1	1*3 0.001						
3	253	0.11 ± 0.91	2*3 0.846	0.14 ± 0.94	2*3 0.726	0.09 ± 0.95	2*3 0.907	35.6 ± 7.3	2*3 0.334	101.0 ± 12.8	2*3 0.885	102.7 ± 12.0	2*3 0.350						
Overall p			0.007		<0.001		0.019		0.011		0.310		0.001						
HDL-C		958																	
1	329	-0.21 ± 0.97	1*2 0.012	-0.16 ± 0.99	1*2 0.047	-0.20 ± 0.97	1*2 0.014	32.6 ± 8.3	1*2 0.186	97.9 ± 16.1	1*2 0.374	96.1 ± 16.5	1*2 0.018						
2	192	0.01 ± 0.91	1*3 <0.001	0.16 ± 0.97	1*3 0.003	0.03 ± 0.97	1*3 <0.001	33.6 ± 8.2	1*3 <0.001	99.1 ± 14.9	1*3 <0.001	99.8 ± 14.5	1*3 <0.001						
3	437	0.06 ± 0.96	2*3 0.525	0.56 ± 0.96	2*3 0.645	0.74 ± 0.97	2*3 0.603	35.5 ± 7.6	2*3 0.007	102.4 ± 12.6	2*3 0.008	102.2 ± 13.2	2*3 0.211						
Overall p			<0.001		0.008		<0.001		<0.001		<0.001		0.001						
Triglycerides		953																	
1	603	-0.02 ± 0.94	1*2 0.909	0.01 ± 0.94	1*2 0.759	0.01 ± 0.99	1*2 0.212	34.8 ± 8.0	1*2 0.023	101.7 ± 13.2	1*2 0.033	101.1 ± 14.1	1*2 0.057						
2	180	-0.03 ± 0.97	1*3 0.120	-0.01 ± 0.99	1*3 0.018	-0.09 ± 0.96	1*3 0.228	33.2 ± 7.8	1*3 0.002	99.1 ± 14.4	1*3 <0.001	98.0 ± 14.3	1*3 <0.001						
3	170	-0.15 ± 1.01	2*3 0.241	-0.20 ± 0.98	2*3 0.090	-0.09 ± 0.99	2*3 0.995	32.6 ± 8.4	2*3 0.454	95.8 ± 17.7	2*3 0.032	95.6 ± 17.0	2*3 0.399						
Overall p			0.290		0.060		0.291		0.002		<0.001		0.001						
Chol:HDL-C		954																	
1	392	0.07 ± 0.98	1*2 0.447	-0.01 ± 0.98	1*2 1.00	0.06 ± 1.00	1*2 0.088	34.8 ± 8.0	1*2 0.040	101.4 ± 13.8	1*2 0.051	100.3 ± 14.9	1*2 1.00						
2	480	-0.04 ± 0.94	1*3 0.019	-0.01 ± 0.98	1*3 0.105	-0.06 ± 0.96	1*3 0.006	33.7 ± 8.1	1*3 0.069	99.5 ± 14.9	1*3 0.053	99.5 ± 14.8	1*3 0.095						
3	82	-0.27 ± 0.92	2*3 0.050	-0.21 ± 0.91	2*3 0.100	-0.28 ± 0.88	2*3 0.064	33.0 ± 8.0	2*3 0.497	98.0 ± 15.3	2*3 0.395	96.3 ± 14.7	2*3 0.258						
Overall p			0.062		0.234		0.015		0.056		0.056		0.097						

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; Chol:HDL-C = cholesterol:HDL cholesterol ratio; NART = National Adult Reading Test; SD = standard deviation.

Lipid levels: 1 – low; 2 – intermediate; 3 – high.

p-values are from ANOVA. Probabilities for significant effects are given in boldface.

Significance at the $p < 0.05$ level.

Table 3. Associations between statin use and cognitive outcomes before and after adjustment for age 11 IQ

	STATIN USERS		NON-STATIN USERS		<i>p</i> FOR DIFFERENCE		ADJUSTED FOR AGE 11 IQ		ADJUSTED FOR AGE 11 IQ AND TC	
	Model 1	Model 2	Model 1	Model 2	β	<i>p</i>	β	<i>p</i> [†]	β	<i>p</i> [§]
Cognitive function	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD						
General (<i>g</i>) ability	–0.16 (0.98)	–0.16 (0.98)	0.09 (0.96)	0.09 (0.96)	–0.121	<0.001	–0.060	0.019	–0.053	0.069
Processing speed	–0.17 (0.95)	–0.17 (0.95)	0.09 (0.95)	0.09 (0.95)	–0.120	<0.001	–0.079	0.006	–0.054	0.104
Memory	–0.17 (1.0)	–0.17 (1.0)	0.07 (0.98)	0.07 (0.98)	–0.079	0.012	–0.019	0.490	–0.022	0.477
Verbal ability	33.2 (8.20)	33.2 (8.20)	35.3 (8.1)	35.3 (8.1)	–0.108	<0.001	–0.053	0.023	–0.051	0.053
Age 70 IQ ^a	98.9 (15.1)	98.9 (15.1)	101.1 (13.7)	101.1 (13.7)	–0.070	0.024	–0.014	0.537	–0.037	0.164
Age 11 IQ	98.3 (15.4)	98.3 (15.4)	100.9 (14.6)	100.9 (14.6)	–0.077	0.015	–	–	–	–

TC = total cholesterol; SD = standard deviation.

Verbal ability – National Adult Reading Test score.

^aAge 70 IQ is age-adjusted (age is not included in these models).*p*-values are from linear regression analyses. Probabilities for significant effects are given in boldface.Significance at the *p* < 0.05 level.[†]Effects adjusted for age 11 IQ.[§]Effects adjusted for age 11 IQ and TC (total cholesterol) levels.**Table 4.** Adjusted effects[†] of serum cholesterol measures on cognitive function scores at age 70 years

	TC			HDL-C			TRIGLYCERIDES			CHOL:HDL-C		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Cognitive function												
General (<i>g</i>) ability	0.099***	0.033	–0.010	0.120***	0.030	0.008	–0.078*	0.008	0.016	–0.061	–0.010	–0.021
Processing speed	0.104***	0.065*	0.028	0.076*	0.005	–0.023	–0.060	0.006	0.015	–0.016	0.038	–0.035
Memory	0.033	–0.043	–0.058	0.117**	0.031	0.029	–0.070*	0.007	0.006	–0.069*	–0.031	–0.032
Verbal ability	0.070*	0.008	–0.020	0.122***	0.024	0.012	–0.101**	0.016	0.026	–0.075*	–0.017	–0.031
Age 70 IQ ^a	0.070*	–0.006	–0.035	0.143***	0.035	0.021	–0.157***	–0.048*	–0.042	–0.085**	–0.017	–0.021

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; Chol:HDL-C = cholesterol:HDL cholesterol ratio.

Model 1: adjusted for sex and age (exact age in days at testing).

Model 2: as model 1 and additionally adjusted for age 11 IQ.

Model 3: as model 2 and additionally adjusted for occupational social class, statin use, and history of cardiovascular disease.

Verbal ability – National Adult Reading Test score.

^aAge 70 IQ is age-adjusted (age is not included in these models).[†]Effect represented as a β (standardized regression coefficient). **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

between cholesterol measures (as continuous variables) and cognitive outcomes at age 70 years, before and after covariate inclusion. In the basic age- and sex-adjusted model (model 1), a higher TC level is associated with better cognitive performance on all cognitive domains: *g* ($R^2 = 0.067$, $p = 0.002$); speed ($R^2 = 0.048$, $p = 0.002$); NART ($R^2 = 0.032$, $p = 0.030$); age 70 IQ ($R^2 = 0.007$, $p = 0.029$) with the exception of memory, and a higher HDL-C level, with better performance on all cognitive outcomes *g* ($R^2 = 0.043$, $p < 0.001$); speed ($R^2 = 0.028$, $p = 0.027$); memory ($R^2 = 0.048$, $p = 0.001$); NART ($R^2 = 0.023$, $p < 0.001$); age 70 IQ ($R^2 = 0.022$, $p < 0.001$). When age 11 IQ is included (model 2), significance is lost for all associations except for TC and processing speed (with marked attenuation; $R^2 = 0.234$, $p = 0.033$) and for all HDL-C associations. In the basic age- and sex-adjusted model (model 1), lower triglyceride levels are associated with better general cognitive ability ($R^2 = 0.033$, $p = 0.016$), memory ($R^2 = 0.041$, $p = 0.032$), verbal ability ($R^2 = 0.019$, $p = 0.002$), and age 70 IQ ($R^2 = 0.027$, $p < 0.001$) and a lower chol:HDL-C ratio with better memory ($R^2 = 0.041$, $p = 0.034$), verbal ability ($R^2 = 0.015$, $p = 0.020$), and age 70 IQ ($R^2 = 0.010$, $p = 0.009$). When age 11 IQ is included (model 2), significance is lost for all associations except for triglycerides and age 70 IQ (with marked attenuation; $R^2 = 0.497$, $p = 0.048$). In the final model, which is adjusted for age 11 IQ, occupational social class, statin use, and history of CVD, significance is lost for all cholesterol-cognitive function associations at age 70 years.

In addition, we ran the same models with social class of origin (based on father's social class) instead of adult social class, in order to examine the potential influence of childhood social circumstances. There were no meaningful differences in results and therefore the data are not shown.

Discussion

In this study, of generally well-functioning older people, we found small but significant associations between serum cholesterol and cognitive functions at age 70 years, almost all of which disappeared after accounting for differences in childhood IQ. Overall, performance on a range of cognitive domains including general (*g*) cognitive ability, processing speed, memory, verbal ability, and IQ at first appeared to be better in those with higher levels of TC and HDL cholesterol and lower levels of triglycerides. However, the key novel finding here was these relationships between cholesterol measures and cognition were markedly attenuated

and mostly no longer significant after including IQ test scores recorded almost 60 years previously. In the final multivariate model, which also included occupational social class, statin use, and CVD history, there was no longer any association between serum cholesterol and cognition. A lower IQ in childhood was related to a higher prevalence of statin use in adulthood. Statin users showed poorer cognitive abilities in old-age independently of earlier ability, but this effect disappeared once we adjusted for serum TC levels. The results suggest that the associations between serum cholesterol, statin use, and cognitive function are confounded by the lifelong stable trait of intelligence. Without early-life measures of intelligence, researchers might attribute a possible causal effect of lipid profiles on successful cognitive aging.

The previous literature on the relationship between serum cholesterol and cognitive outcomes in later-life is equivocal, probably in part due to age-effects. Some reports suggest that the impact of lipids on cognitive trajectories is most prominent in mid-old age. But, over the age of 65 years, serum lipids have little predictive value in terms of cognitive outcomes (Mielke *et al.*, 2008; Van Vliet *et al.*, 2009; Reynolds *et al.*, 2010; Formiga *et al.*, 2011; 2012; Van Vliet, 2012). Our finding of poorer performance in those with lower TC is consistent with previous studies demonstrating similar results (e.g. Karlamangla *et al.*, 2004; van den Kommer *et al.*, 2009). However, in terms of cardiovascular risk, "low" cholesterol levels are considered to be "desirable." Given that assessment occurred later in life in the present sample, the finding of increased prevalence of disease (including high cholesterol) and statin use (about 50%) in those with the lowest TC levels, probably reflects the beneficial effect of cholesterol reduction with statin treatment over a period of time. Elevated cholesterol levels at this stage in life may not be a good indicator of cognitive function or predictor of subsequent cognitive decline. In the current sample of 70-year-olds, lipid measures were clearly associated with a range of cognitive outcomes including processing speed, verbal ability, and general (*g*) cognitive ability, but this effect often went away after including childhood intelligence. One of the key findings here is that childhood intelligence accounts for much of the initially reported association between TC, HDL-C, triglycerides, and cognitive abilities. The LBC1936 Study is useful in having intelligence data from youth as it is rarely available. Without it the results could have been interpreted as suggesting a possible role for higher cholesterol levels in successful cognitive aging.

Why would there be a life-long relationship between intelligence and serum lipid profiles?

Intelligence and health are inextricably linked across the life course. The relationship between lifestyle factors and cognitive abilities is well-documented (Hertzog *et al.*, 2009; Lee *et al.*, 2010). Crucially, intelligence from childhood is associated with health behaviors including diet, physical exercise, smoking, and alcohol consumption, and, pathways linking childhood IQ and lifestyle involve reciprocal interactions. Gottfredson (2004) suggested that IQ may be the single most important factor in the adoption of such health behaviors in adulthood. This may, in part, explain the well-documented relationship between low childhood IQ and high morbidity rates (Calvin *et al.*, 2011) resulting in increased medication use in later life including statins (Starr *et al.*, 2004). The higher prevalence of statin use in those with lower intelligence scores from childhood in the current sample attests to this.

Although genetic predisposition and metabolic function largely determine an individual's serum lipid profile, lifestyle-related factors may influence serum cholesterol. For example, low nutritional intake, weight loss, and poor overall health, are features more likely to be present in those with a low IQ and SES given the intelligence and SES gradients in health. Dietary (macronutrient) intake is known to affect lipid levels (Cook, 2005), and the brain, which is the most cholesterol-rich organ in the body, is vulnerable to such diet-induced changes in serum lipid levels (Muldoon *et al.*, 1997; Thorsson *et al.*, 2013). In addition to dietary intake, research suggests that physical activity (Bronwell *et al.*, 1982; Ellison *et al.*, 2004), moderate alcohol consumption, and non-smoking (Whitehead *et al.*, 1996; Ellison *et al.*, 2004) are related to increases in HDL cholesterol. An increased BMI (Ellison *et al.*, 2004) and fat mass decreases HDL cholesterol (Schubert *et al.*, 2006).

In the present study, the relationship between some health-related behaviors such as dietary saturated fat and dietary cholesterol intake, adherence to a "healthy" Mediterranean-style dietary pattern, and alcohol consumption with TC levels was not clear-cut and at times, counter-intuitive. The TC-diet findings may be suggestive of behavioral change in those with or at high-risk of CVD. Dietary advice usually accompanies a diagnosis of high cholesterol by a medical practitioner; dietary intervention is increasingly recognized as a necessary strategy against various metabolic disorders. Advice regarding dietary fat quality, in particular, the inclusion of foods rich in PUFAs (including oily fish), at the expense of foods high in saturated fats and dietary cholesterol, has been shown to have cardioprotective effects by improving serum lipid profiles (Sacks, 1994).

In a summary of the largest primary and secondary dietary prevention studies, Law *et al.*, (1994) estimated that for a 10% reduction in serum cholesterol (0.6 mmol L), the risk of non-fatal myocardial infarction was reduced by 9% in the first two years of follow-up, 14% from years two to five, and by 37% with more than five years of follow-up. In the current sample, the low-TC group had the highest prevalence not only of CVD but stroke, hypertension, statin use, and high BMI, and therefore the most likely group to have made dietary modifications as part of a health management program to reduce weight and improve overall health. However, TC represents many sub-components including HDL, LDL, and very-LDL cholesterol, and therefore the effect of a dietary change on TC may differ depending on which specific cholesterol components were altered (Willett, 2012). Furthermore, we suggest that these behavioral modifications are relatively recent otherwise we would have expected TC levels to be affected by a low cholesterol diet; a finding not borne out of our results. This possibly reflects relatively recent interest in potential adverse effects of high dietary cholesterol on older adults among GPs and other medical practitioners. However, those with the highest TC had a lower BMI, more physically active lifestyles and were less likely to be current smokers. Such evidence may support the theory that the relationship between childhood IQ, serum lipid profiles, and necessity of lipid-lowering medication, is mediated by lifestyle factors and the possibility of reverse causation, that is, higher lifetime trait levels of IQ predict lipid profiles in adulthood (via lifestyle), rather than lipid profiles predicting IQ/cognitive ability. Alternatively, any relationship between serum cholesterol and intelligence may originate in childhood when the developing brain is more susceptible to environmental influences such as nutrient supply.

The results do not support an effect (beneficial or detrimental) of statins on cognition. Although initial analyses revealed some differences favoring non-statin users in terms of better cognitive function, adjusted analyses suggested that participants taking statins did not differ from their counterparts in terms of neuropsychological test performance. Our results are in line with another observational study (Benito-León *et al.*, 2010) and several clinical trials (Trompet *et al.*, 2010; see Xiong *et al.*, 2005) reporting no cognitive effects of statin treatment in the elderly, but not with the many observational studies reporting beneficial effects (Rockwood *et al.*, 2002; Yaffe *et al.*, 2002; Bernick *et al.*, 2005; Solomon *et al.*, 2009). On the whole, longitudinal studies with long follow-up periods have failed to

confirm these results (see Van Vliet *et al.*, 2009) and a recent systematic review of randomized controlled trials, cohort case-control, and cross-sectional studies evaluating cognition in patients receiving statins concluded that statins have a neutral effect. However, the lack of cognitive benefit in old age does not obviate that use of statins in middle age might be beneficial for cognitive function later in life.

Those who survive to old age with high cholesterol may be physically more robust and less susceptible to the adverse effects of a high midlife TC on cardiovascular pathologies. Alternatively lower TC levels in elderly people may be a proxy for poorer general health status and/or malnutrition (Brescianini *et al.*, 2003). There is some suggestion that TC may be a potential marker of physical frailty (Schalk *et al.*, 2004, Tilvis *et al.*, 2011). In the current study, a low TC level, compared to both intermediate and high levels was associated with an increased prevalence of a range of diseases. Approximately half of those in the lowest TC group had a history of stroke, hypertension, and lipid-lowering medication use, and 40% had CVD thus supporting the latter suggestion. Higher cholesterol levels in the elderly are inversely associated with the onset and outcome of certain diseases (Onder *et al.*, 2003), better health outcomes after stroke (Dyker *et al.*, 1997) and surgery (Delgado-Rodriguez *et al.*, 2002). Total cholesterol is an independent predictor of all-cause mortality in middle-age but in those over the age of 65 years, high cholesterol levels provide a mortality advantage over lower levels (Weverling-Rijnsburger *et al.*, 1997; Schatz *et al.*, 2001). We suggest that higher total serum cholesterol levels reflect better health status in late-life and are therefore likely to associate with better physical health markers but there is no evidence that lipid profiles contribute independently to cognitive aging, successful or otherwise.

Study strengths and limitations

This is, to our knowledge, the first study to examine the relationship between serum cholesterol and cognition that also includes a validated measure of early-life IQ. In terms of cognitive ability, it was useful to have measures at two distant points across the life course. Knowledge of cognitive ability before the influences of aging and illnesses is necessary in order to elucidate possible causal directions because lower childhood IQ is in itself related to a greater risk of disease and a higher mortality (Whalley and Deary, 2001, Calvin *et al.*, 2011). Other large cohorts might look, in the future, at prior cognitive ability measurements at multiple time-points. Given the stability of intelligence (Deary *et al.*, 2000),

results may not differ significantly. The large sample size and availability of comprehensive cognitive, health, and demographic data were important for statistical power and to determine whether cholesterol contributes to the variance in cognitive scores explained by “extrinsic” factors, given that approximately half the variance in IQ scores in old age is explained by childhood IQ (Deary *et al.*, 2000). We examined multiple cholesterol measures. Participants were from a narrow age range, thereby minimizing the confounding effect of chronological age differences.

The cross-sectional design of this study – albeit with a much earlier measure of cognitive ability – is a limitation as it is possible that current lipid levels may reflect recent changes in response to poor physical health, i.e. underlying disease or weight loss with age, in addition to widespread statin use, rather than lipid history. However, future longitudinal analyses on the LBC1936 within old age (using baseline age 70 data) are planned, with cognitive, lipid, and dietary data collection prospectively over several waves of follow-up spanning ten years. There is a possibility that individuals with high midlife serum cholesterol succumb to its adverse biological effects and die before they reach the age 70 years. An older, and relatively healthy cohort such as the present sample, may represent a select group with lower cholesterol, on average, than the general population of the same age. Whereas it is not possible to determine the pattern of lipid levels before older age in this sample, this does not affect our conclusion that there is little direct relationship between lipids and cognitive function in later-life. Pattern of TC change may be more relevant to late-life cognition than TC levels at given time points. We had no measure of LDL cholesterol, although we utilized the cholesterol:HDL cholesterol ratio as a proxy measure. Blood samples in this study were measured in the non-fasting state which might influence the concentrations of cholesterol. However, a growing body of evidence suggests that fasting is not necessary prior to a lipid test in most scenarios as it does not greatly alter the levels of lipid parameters (Gaziano, 2012). Non-fasting lipid profiles change minimally in response to food intake in the general population (Langsted *et al.*, 2008). The authors are confident that the use of a non-fasting blood sample is more than sufficient to examine population variations in cholesterol parameters in a relatively healthy, community dwelling sample such as the LBC1936.

We used a self-report dietary assessment instrument (FFQ) which may be subject to misreporting of food intakes. However, the (self-selected) LBC1936 consists of relatively healthy, high-functioning men and women, and the

empirical outcome of any non-systematic (low-level) misreporting is likely to be, at most, a small amount of noise in the data. Moreover, the SCG-FFQ used in the present study, shows good repeatability (dietary intake in later life is reasonably stable in the short term) and validity in community-dwelling older populations compared with four-day diet diaries (Jia *et al.*, 2008; McNeill *et al.*, 2009).

Finally, these simple indices of cholesterol are fairly “coarse” measures. We have not taken into account individual fatty acids. There is evidence that unsaturated fatty acids have a major benefit on cognition (Whalley *et al.*, 2004). Future examination of such dietary factors (including individual fatty acids) on TC sub-components, i.e. individual lipid indices such as HDL, LDL, and very-LDL, and cognition, may be warranted.

Conclusions

In this community-based sample of older men and women, higher cholesterol (TC and HDL-C) and lower triglycerides levels were not associated with better cognition once the confounding effects of childhood IQ were taken into account. We conclude that serum lipid profiles do not independently contribute to cognitive aging, successful or otherwise, in this cohort. Further studies are required to determine the longitudinal relationships between changes in lipid levels and changes in cognitive function and decline in the same samples and to determine the pathways linking early-life cognitive ability with serum cholesterol in later life.

Conflict of interest

None.

Description of authors' roles

J. Corley was involved in data collection, performed the statistical analyses, and led the writing of the paper. J. Corley and I. J. Deary discussed the statistical analyses. I. J. Deary and J. M. Starr contributed to study design, study management, interpretation of analyses, and drafting of the manuscript.

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BRIEF REPORT

Reverse Causation in Activity-Cognitive Ability Associations: The Lothian Birth Cohort 1936

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Active lifestyles might protect cognitive abilities; however, studies rarely consider the reverse causal direction. Activity-cognition associations might reflect stable intelligence differences rather than a protective effect of activity. The Lothian Birth Cohort 1936 ($n = 1091$) completed cognitive tests aged 70, having taken an intelligence test aged 11. Activity (assessed by participation in 15 activities that produced a socio-intellectual activity factor, and by physical activity) was positively associated with cognition ($r = .08$ to $.32$, $p \leq .05$). When age-11 IQ and adult social class were controlled, only physical activity remained significantly associated with general cognitive ability and processing speed.

Keywords: prior cognitive ability, cognitive ability, activity participation, physical activity, reverse causation

Examining for any cognitively beneficial effect of adopting an active and engaged lifestyle has become a key focus in cognitive aging research on the principle that activity participation is potentially modifiable (Hertzog, Kramer, Wilson, & Lindenberger, 2009; Anstey & Christensen, 2000). However, findings are prone to the possibility of reverse causation: prior intelligence is likely to predict the choice of leisure-time pursuits, particularly whether to engage in those of a mentally stimulating or demanding nature. The current study investigated associations between activity and cognitive abilities in old age before and after adjustment for this possible confounding variable.

Fratiglioni, Paillard-Borg, & Winblad (2004) reviewed 15 longitudinal studies investigating the effects of lifestyle factors on

normal cognitive aging, grouped according to whether they assessed social networks, physical activity, or nonphysical activity. They concluded the following: “for all three lifestyle components (social, mental, and physical), a beneficial effect on cognition . . . [is] suggested” (p. 343). A recent comprehensive state-of-science review by Hertzog et al. (2009) provides a detailed critique of the literature on lifestyle factors and their likely role as cognitive enhancers, and supports the general hypothesis of the benefits of primarily intellectual and physical activities. The current paper will not review this literature but rather will begin with the reported positive effects of activity participation across domains and examine these within the context of prior cognitive ability.

Of the studies included in Fratiglioni, Paillard-Borg, & Winblad (2004), eight examined the link between (mostly) self-reported physical activity and cognition. All but one reported an association between increased physical activity participation and better cognitive function or less cognitive decline. The protective effect on cognition came from moderate and strenuous physical activity (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001), including walking (Weuve et al., 2004). As walking is the most common exercise taken by older individuals (World Health Organization, 1998), a beneficial effect of this simple, low-cost workout would potentially be among the most straightforward to influence (Yaffe et al., 2001).

Social activities, such as visiting friends and family, were also considered. Although Fratiglioni and colleagues (2004) suggested there was evidence for a beneficial effect of improved social networks on cognitive function, the boundaries between social activity and social support networks were often blurred by the nature of assessing them. Researchers investigating social support often include basic measures of social activity participation in their indices (such as church membership or participation, for example), and vice versa. Is it something of the social activity or the support received during such interaction that is potentially important?

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Because it is hard to define a purely social activity, there are fewer studies in this domain compared with intellectual and physical pursuits (similarly, “physical” activities could involve social support, intellectual effort, etc.). Consequently, results in this domain have been more difficult to synthesize (Hertzog et al., 2009).

The assessment of nonphysical leisure activities generally consists of pursuits thought to stimulate an individual cognitively, specifically requiring mental, as opposed to social or physical, engagement (Fratiglioni, Paillard-Borg, & Winblad, 2004). Mental engagement activities, and perhaps specifically activities involving novel information processing such as playing bridge or learning a language (Hultsch, Hertzog, Small, & Dixon, 1999), are often presented as the most important with respect to the preservation of cognitive abilities into old age, frequently expressed within the “use it or lose it” hypothesis (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). Hertzog et al. (2009) have argued that the consistency in findings across diverse studies suggests the “underlying association is quite robust” (p. 23). Yet, the direction of causation remains a prime concern; “cross-sectional relationships may indicate simply that brighter and more educationally advantaged people are more likely to participate in intellectually demanding pursuits” (Hultsch et al., 1999, p. 260). Studies with follow-ups in later life are supportive of a beneficial effect of engagement (Lovden, Ghisletta, & Lindenberger, 2005; Ghisletta, Bickel, & Lovden, 2006), although rarely is the possibility of reverse causation addressed.

Investigating the likelihood of reverse causation in the activity literature is of central importance. The possibility that the cross-sectional association between increased activity and improved cognitive performance might be wholly or partly attributable to prior cognitive ability predicting both has implications for those developing activity-based interventions to reduce cognitive decline. Hultsch et al. (1999) proposed that insufficient attention has been paid to the possibility that cognitive decline may influence engagement, as opposed to vice versa, and that many studies have too readily accepted the use it or lose it assumption. Studies able to control for prior intelligence—and thus investigate reverse causation—although rare, are necessary. Richards, Hardy, & Wadsworth (2003) suggested that, independent of childhood ability, active leisure-time was beneficial for the level of memory function, while physical activity prevented decline over 10 years. By being able to adjust for childhood ability, the results were less likely to be a consequence of reverse causation and suggested that differential effects of activity types might be detectable.

Given the potential for reverse causation in this domain, it is worryingly underreported. Although a recent review highlighted seven unanswered questions within the context of the engagement hypothesis of cognitive aging (Bielak, 2010), it did not address this issue (a brief mention was made of the difficulty of assigning a causal direction to any association discovered in old age).

Studies often assess multiple activity domains. However, they are generally analyzed separately to discover whether one form of activity might confer greater protection and represent the most appropriate target for any future interventions, or whether different domains of cognitive function might be differentially associated with different domains of activity (Bielak, 2010). Because many activities cross domains, some researchers have shifted from attempts to assess “social” activities, and “intellectual” activities, and “physical” activities, to assessing activity more generally

(Karp et al., 2006; Bielak, 2010). It is worth examining patterns in the way individuals are active and how activity in general might be beneficial in terms of health and well being.

Present Study

Whereas most of the studies examining the association between activity participation and cognitive abilities report a positive association, support for the engagement hypothesis is by no means universal. The conclusion to the Fratiglioni, Paillard-Borg, & Winblad (2004) review asked the following:

Can . . . premorbid intelligence explain the reported associations? . . . Is the cognitive stimulation the common factor for all investigated lifestyles? Which is the most relevant component: physical, cognitive, or social? How do they interact? (p. 351)

Data from the Lothian Birth Cohort 1936 were used to address these issues, namely the following: how are activity domains best considered (separately or by some composite)?; is cognitive ability in childhood related to activity participation in old age?; independently of childhood mental ability, does activity participation affect the level of ability in later life?

Method

Participants

The recruitment and testing of the Lothian Birth Cohort 1936 (LBC1936) has been described extensively (Deary et al., 2007; Deary, Whalley, & Starr, 2009). In total, 1091 relatively healthy participants (548 men and 543 women) were tested at a mean age of 69.5 years old ($SD = 0.8$). Only variables relevant to the current analysis are reported in detail; further information can be obtained from Deary et al. (2007).

Cognitive Testing

The LBC1936 participants completed the Moray House Test (MHT) at a mean of 10.9 years ($SD = 0.3$) (Scottish Council for Research in Education, 1949). Participants repeated the MHT at age 70. Scores were corrected for age in days at time of completion and converted to an IQ-type scale ($M = 100$, $SD = 15$). At age 70, participants completed a battery of psychometric cognitive tests selected from the Wechsler Adult Intelligence Scale (WAIS)-III U.K. (Wechsler, 1998a) and Wechsler Memory Scale (WMS)-III U.K. (Wechsler, 1998b), with the addition of reaction time (Cox, Huppert, & Whichelow, 1993) and inspection time (Deary et al., 2004) for processing speed. Principal Components Analysis (PCA)-derived scores were computed for general cognitive ability, memory, and processing speed (Luciano et al., 2009; Corley et al., 2010). Participants also completed the National Adult Reading Test (NART; Nelson & Willison, 1991) and the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001), frequently used estimates of peak cognitive ability.

Activity Questionnaire

Items concerning physical, mental, and social activities were included in a questionnaire (984 questionnaires were received).

Participants were asked: "What level of physical activity do you mainly do?", answered on a six-point scale: 1) moving only in connection with necessary (household) chores, 2) walking or other outdoor activities 1–2 times per week, 3) walking or other outdoor activities several times per week, 4) exercising 1–2 times per week to the point of perspiring and heavy breathing, 5) exercising several times per week to the point of perspiring and heavy breathing, 6) keep-fit/heavy exercise or competitive sport several times per week (adapted from Hirvensalo, Lampinen, & Rantanen, 1998). Participants were also given a list of 15 activities (e.g., "Reading a book" and "Visits to friends or family"; full list on request) drawn from those commonly used in previous work (i.e., Hultsch et al., 1999; Richards, Hardy, & Wadsworth, 2003; Wilson et al., 2002; Wilson, Barnes, & Bennett, 2003; Glass, de Leon, Marottoli, & Berkman, 1999) and instructed as follows: "For each activity in the list, mark an 'X' to show how often you generally do it now." Answers were on a five-point scale, from "every day or about every day" to "less than once a year/never," assigned values of 5 to 1, respectively.

Results

PCA of Activity Items

A PCA was conducted on the 15 activity items. The KMO Measure of Sampling Adequacy (MSA: Kaiser, 1974) was .72. The item "Going to pubs or social clubs" had an MSA of .41. When the PCA was rerun with this item removed, the new overall MSA was .75 and all items had values above .50. Examination of the scree plot suggested the extraction of a single component accounting for 19.6% of the variance (item loadings on this first unrotated component available on request). All items loaded positively except "Watching TV" (–.21). An activity factor—named socio-intellectual activity—was produced by summing the 11 items with loadings greater than .30, with a Cronbach's alpha = .66.

Descriptives

Nine hundred thirty-four participants had a score for socio-intellectual activity, and 961 answered the question about physical activity. In terms of physical activity, responses ranged from "moving only in connection with necessary (household) chores" (1) to "keep-fit/heavy exercise or competitive sport several times per week" (6), with a mean of 2.98 ($SD = 1.11$), corresponding to "walking or other outdoor activities several times per week." The number of participants in each category were as follows: 1 = 88, 2 = 175, 3 = 499, 4 = 100, 5 = 69, 6 = 30. Scores on the socio-intellectual activity factor ranged from 11 to 44, with a mean of 25.94 ($SD = 5.11$). There was a small, significant association between socio-intellectual activity and physical activity ($r = .17$, $p < .001$). Men were more physically active than women [3.08 ($SD = 1.09$) versus 2.88 ($SD = 1.11$); $t(959) = -2.729$, $p = .006$]. Women had higher scores on the socio-intellectual activity factor [27.13 ($SD = 4.99$) versus 24.71 ($SD = 4.92$) for men; $t(932) = -7.458$, $p < .001$].

Associations Between Activity and Cognitive Ability

The correlations between the activity and cognitive measures are shown in Table 1. Socio-intellectual activity was significantly positively associated with all cognitive outcomes at age 70, ranging from .19 with processing speed to .32 with NART. Age-11 IQ was also associated with socio-intellectual activity ($r = .30$). All associations were attenuated to nonsignificance when repeated with age-11 IQ partialled out, except activity-NART/WTAR (which were reduced to .20 and .13, respectively). Physical activity was significantly positively associated with all of the cognitive outcomes (see Table 1), ranging from .07 with NART to .14 with general cognitive ability and processing speed. The age-11 IQ-physical activity correlation was .08. When age-11 IQ was partialled out, the physical activity-memory and physical activity-NART correlations became nonsignificant although virtually unaltered in terms of magnitude; the remaining associations were almost unaltered.

Table 1
Correlations Between Activity and Cognitive Abilities in the Lothian Birth Cohort 1936

	Socio-intellectual activity			Physical activity		
	Age-11 IQ partialled	Percentage shared variance before/after age-11 IQ adjusted (% attenuation)		Age-11 IQ partialled	Percentage shared variance before/after age-11 IQ adjusted (% attenuation)	
Age-11 IQ	.30***	—	—	.08*	—	—
Age-70 IQ	.23***	.04	5.29/0.16 (97%)	.10**	.10**	1.00/1.00 (0%)
General cognitive ability	.21***	.02	4.41/0.04 (99%)	.14***	.12**	1.96/1.44 (26%)
Processing speed	.19***	.05	3.61/0.25 (93%)	.14***	.15***	1.96/2.25 (NA)
Memory	.21***	.06	4.41/0.36 (92%)	.08*	.07	0.64/0.49 (23%)
NART	.32***	.20***	10.24/4.00 (61%)	.07*	.06	0.49/0.36 (26%)
WTAR	.27***	.13***	7.29/1.69 (77%)	.08*	.08*	0.64/0.64 (0%)

Note. Correlations are raw and with age-11 IQ partialled. $n = 885$ – 960 ; for the partial correlations, all $n = 778$. Age-11/70 IQ = raw age-11/70 MHT score corrected for age in days at time of testing and converted into IQ scores (by definition, age-11/70 IQ has a mean of 100 and a standard deviation of 15). General cognitive ability = 1st unrotated component from a PCA of symbol search, digit symbol, matrix reasoning, letter number sequencing, backwards digit span, and block design; Processing speed = 1st unrotated component from a PCA of symbol search, digit symbol, choice reaction time, inspection time, simple reaction time (log 10 transformed); Memory = 1st unrotated component from a PCA of logical memory immediate recall, logical memory delayed recall, spatial span forwards, spatial span backwards, verbal paired associates immediate recall, verbal paired associates delayed recall, letter number sequencing, and backwards digit span; NART = National Adult Reading Test; WTAR = Wechsler Test of Adult Reading.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Separate general linear models were run for each of the cognitive outcomes as the dependent variable and either socio-intellectual activity or physical activity as the independent variable (see Table 2). There was a small but significant positive association for all cognitive outcomes with socio-intellectual activity when age and sex were controlled, accounting for 3.4 to 9.9% of the variance. Adjusted for age-11 IQ, all associations were reduced to nonsignificant levels and the variance accounted for by socio-intellectual activity was reduced to less than 0.5% across all cognitive outcomes except processing speed, NART, and WTAR (socio-intellectual activity accounted for 0.5–3.5% of the variance). Only the latter two effects remained when all covariates were included: socio-intellectual activity accounted for 2.0% of the variance in NART performance and 0.5% in WTAR.

In terms of physical activity, there were positive associations with all the cognitive outcomes in the initial age- and sex-adjusted models, accounting for 0.5 to 1.9% of the variance (see Table 2). However, additionally adjusting for age-11 IQ resulted in attenuation of many of the associations. Using age-70 IQ as an example, physical activity accounted for about 1% of the variance, which was reduced to about 0.3% with age-11 IQ included. Including all covariates, physical activity was positively associated with general ability and processing speed, accounting for about 1% of the variance in each.

Discussion

In the LBC1936, higher childhood cognitive ability was associated with being more active at age 70, either physically ($r = .08$) or in terms of a social-intellectual activity score ($r = .30$). Although both measures of activity were cross-sectionally associated with better cognitive functioning at age 70, age-11 IQ generally accounted for almost all of the association between sociocultural activity and the cognitive outcomes. After adjusting for childhood intelligence, participants with higher socio-intellectual activity scores performed better on tests of vocabulary, whereas increased physical activity remained associated with higher performance in terms of general cognitive ability and processing speed.

Hertzog et al. (2009) concluded that when assessed alongside other lifestyle factors, “cognitive activities appear to be the strongest predictor of cognitive change” (p. 39). To assert that activity is cognitively advantageous these effects must persist after a valid measure of prior cognitive ability is accounted for (Deary & Gow, 2008). It is interesting that prior cognitive function is less associated with physical activity in later life than with a variety of social and intellectual pursuits. The results suggest, in later life at least, such cultural activities might reflect an outward manifestation of cognitive ability, rather than conferring any special advantage in terms of current or future cognitive status. Physical activity is, perhaps, a preferred target in terms of developing interventions to reduce cognitive decline. Previous research has highlighted the cognitive benefit of even light and moderate exercise (Yaffe et al., 2001; Weuve et al., 2004). Many putative protective lifestyle factors are highly confounded by earlier demographic factors; those lifestyle factors confounded to a lesser degree must be identified and pursued.

The current results underscore the notion that many studies reporting a cognitively protective effect of activity participation may be stating no more than that individuals of higher ability are

Table 2
Summary of General Linear Models for the Association Between Activity and Cognitive Abilities in the Lothian Birth Cohort 1936

Independent variable	Model covariates	Age-70 IQ		General cognitive ability		Processing speed		Memory		NART		WTAR	
		p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2	p	η_p^2
Socio-intellectual activity	Age + sex	<.001	.061	<.001	.049	<.001	.034	<.001	.037	<.001	.099	<.001	.069
	Age + sex + age-11 IQ	.060	.004	.076	.004	.035	.005	.202	.002	<.001	.037	.001	.014
	Age + sex + age-11 IQ + social class	.395	.001	.702	.000	.314	.001	.585	.000	<.001	.020	.046	.005
Physical activity	Age + sex	.002	.010	<.001	.019	<.001	.019	.012	.007	.029	.005	.011	.007
	Age + sex + age-11 IQ	.100	.003	.003	.010	.001	.013	.236	.002	.397	.001	.233	.002
	Age + sex + age-11 IQ + social class	.194	.002	.011	.007	.004	.010	.288	.001	.899	.000	.577	.000

Note. The p value and associated partial eta squared (η_p^2) show the effect of socio-intellectual activity/physical activity in the model. Significant results are highlighted in bold. Also see note Table 1. Participants reported their highest occupational position achieved, and for married women, that of their spouse. This was assigned a social class from I, professional, to V, unskilled (class III being divided into IIIN and IIIM, nonmanual and manual, respectively) according to the 1951 Classification of Occupations (General Register Office, 1956). Married women were assigned whichever was the highest of their own or their husband's social class.

more likely to participate in social and intellectual pursuits (Hultsch et al., 1999). Associations in later life may be derived from the lifelong stable trait of intelligence, not an independent contribution from activity and engagement. That said, activity participation did account for variance in the tests of adult reading (Nelson & Willison, 1991; Holdnack, 2001). These are frequently used as proxies when a measure of actual prior ability is unavailable, specifically as indicators of maximal or peak ability. The association of activity participation with these measures may suggest that general engagement in social and intellectual pursuits predicts the peak level of cognitive ability achieved in adulthood, consistent with Richards, Hardy, & Wadsworth (2003). The current study is unable to ascertain a causal pathway because of the timing of assessments; both activity and cognitive assessments were conducted when the participants were a mean of 70 years. However, there are plausible mechanisms (environmental complexity, e.g., Schooler, 1984), but it is uncertain whether this active engagement would be required during critical developmental periods, or whether there is a continued effect (Anstey & Christensen, 2000).

The cognitive stimulation resulting from increased activity is often suggested as key to any protective effect. Activities which are specifically cognitive, or those from other domains necessitating some level of cognitive engagement, may act through a shared pathway. An engagement model of cognitive level and decline proposes those more engaged with their environment are less likely to suffer the adverse effects of cognitive aging or at least delay the onset of such age-related cognitive decline (Anstey & Christensen, 2000; Kramer et al., 2004). With a (dis)engagement model, however, the nature of causality is difficult to tease out, particularly as participation in cognitively demanding activities is determined by prior cognitive ability (Hultsch et al., 1999). The LBC1936 results are tentatively consistent with the proposal that cognitive and social activities may contribute to the maximal level of cognitive ability achieved, although the present data cannot be conclusive. Unfortunately, if any accrued benefit of activity and engagement needs to be assessed earlier in life, further waves of cognitive and activity assessment will not allow this to be investigated. Methods including retrospective reports (Fritsch et al., 2007) will need to be explored.

Physical activity was found to predict general cognitive performance and processing speed after controlling for social class and prior cognitive ability, accounting for about 1% of the variance in each. This is consistent with previous research; for example, women who walked more when aged about 70 years old were less likely to experience cognitive decline over the subsequent 7 1/2 years (Yaffe et al., 2001). Data from the 2009 Scottish Household Survey reported walking as the most common form of exercise taken by older adults: in the 60 to 74 years old category, 53% walked for at least 30 minutes for recreational purposes in the previous four weeks (The SHS Team, 2010).

Further investigation is especially important as van Gelder et al. (2004) reported that decreasing physical activity was detrimental to cognitive health. Physical activity could lead to improved cognitive function via better health and a lower burden of disease, with subsequent consequences for healthier brain function, or act as a marker for a generally healthy lifestyle with the associated reduction in illness and infirmity. As vascular disease has been linked to cognitive decline and Alzheimer's, increased physical activity may

therefore have a beneficial effect on later life cognitive outcomes via a reduction in vascular risk factors (Hendrie et al., 2006). It has also been proposed that physical activity may have a direct effect on brain structure or physiology (van Gelder et al., 2004; Yaffe et al., 2001; Fratiglioni, Paillard-Borg, & Winblad, 2004; Hendrie et al., 2006; Dishman et al., 2006).

Limitations

The measures used, particularly for physical activity, were relatively crude (though comparable to the previous research from where they were derived). It would be advantageous to also consider other aspects of physical activity (type, intensity and duration, energy expenditure) to more precisely index the physical activity required to produce a beneficial effect on cognition. Other activities were not grouped specifically as social or intellectual as many activities are likely to include social *and* intellectual engagement. Extracting a latent activity factor limits the possibility of deciding what particular activities within this might be driving any activity-cognition associations; however, the social versus intellectual division might be something of a false separation driven by expectation rather than empirical data (Bielak, 2010). The first unrotated component provided an overall activity measure which may be more informative of how people actually go about their leisure time. In addition, the mechanisms proposed to account for the benefits of social and intellectual activities overlap to an extent and are not mutually exclusive.

The LBC1936 is purely observational. Activity patterns occur within a milieu of social and health behaviors not accounted for in the current study; if these explain any protective effects, interventions may fail to provide a benefit. Further, the LBC1936 follow-up began at age 70. To be of benefit to cognitive function in the eighth decade, activity participation may need to be initiated and maintained decades before (Fritsch et al., 2007; Richards, Hardy, & Wadsworth, 2003). Finally, the study is primarily cross-sectional and cannot account for the causal direction of the effects reported. Follow-up at age 73 is ongoing, and planned for age 76. These waves will allow examination of whether activity participation at age 70 is associated with the trajectory of cognitive change. Although similar to the current examination, level of cognitive ability at a given age and change across time are distinct.

Conclusions

If lifestyle variables—including activity participation—have a positive impact upon cognitive aging, such findings are of great importance, perhaps more so than genetic or biological influences, because they may be “more directly amenable to psychological intervention” (Schaie, 1984, p. 476). The assessment of activity participation in the Lothian Birth Cohort 1936 suggests that general activity and engagement may contribute to the development of peak cognitive ability in adulthood, whereas physical activity may continue to predict cognitive abilities in old age. Further work will investigate the effect of activities through the 70s.

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Appendix B - Other Publications 2009 – 2015

Age-associated cognitive decline

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Introduction: Age-associated cognitive decline—or normal (non-pathological, normative, usual) cognitive ageing—is an important human experience which differs in extent between individuals. The determinants of the differences in age-related cognitive decline are not fully understood. Progress in the field is taking place across many areas of biomedical and psychosocial sciences.

Areas of agreement and controversy: The phenotype of normal cognitive ageing is well described. Some mental capabilities are well maintained into old age. From early adulthood, there are declines in mental domains such as processing speed, reasoning, memory and executive functions, some of which is underpinned by a decline in a general cognitive factor. There are contributions to understanding individual differences in normal cognitive ageing from genetics, general health and medical disorders such as atherosclerotic disease, biological processes such as inflammation, neurobiological changes, diet and lifestyle. Many of these effect sizes are small; some are poorly replicated; and in some cases, there is the possibility of reverse causation, with prior cognitive ability causing the supposed 'cause' of cognitive ability in old age.

Emerging areas for developing research: Genome-wide scans are a likely source to establish genetic contributions. The role of vascular factors in cognitive ageing is increasingly studied and understood. The same applies to diet, biomarkers such as inflammation and lifestyle factors such as exercise. There are marked advances in brain imaging, affording better *in vivo* studies of brain correlates of cognitive changes. There is growing appreciation that factors affecting general bodily ageing also influence cognitive functions in old age.

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Introduction

The impact of age itself on cognition—not dementia, and not mild cognitive impairment, nor the other specific cognitive decline syndromes—is such a large, immediate problem for current science, and so ignored by current scientists, that Brayne¹ called it, ‘the elephant in the room’.

With an increasingly aged population, both in the UK and internationally, cognitive impairment is a major health and social issue. Cognitive decline is among the most feared aspects of growing old. It is also the most costly, in terms of the financial, personal and societal burdens. It is important, because cognitive decline heralds dementia, illness and death. In the UK, cognitive failure is the cause for 40% of admissions to institutional care. It is widely agreed that more research is needed to understand the mechanisms of cognitive ageing and the factors that contribute to its individual differences.¹ Committees have been formed, and book-length calls have gone out from national organizations, enumerating the problems of the ageing brain and the necessary research agenda: from the Scottish National Health Service,² from the UK’s House of Lords,³ from the USA’s National Academies⁴ and the USA’s National Institutes of Health.⁵ The latter stated that, ‘identifying the demographic, biological, and psychosocial factors that can help people maintain or enhance their cognitive and emotional health as they grow older becomes a major public health goal for this country’ (p. 13). The present summary of some aspects of non-pathological cognitive ageing focuses on studies that have examined older people. However, the state of the brain in old age is the summary of effects across the lifecourse, from conception. This long view is well represented in the UK Government Office for Science’s Foresight Report, ‘Mental Capital and Wellbeing’,⁶ and it is highly recommended.

The above-mentioned sources^{1–6} on cognitive ageing and its causes make it clear—to a greater or lesser extent—that it is far from straightforward to separate non-pathological from pathological cognitive decline. Often, in the studies that are summarized below, this is done by brief tests such as the Mini-Mental State Examination and/or by the absence of a clinical diagnosis, and sometimes by exclusion using a standardized psychiatric interview. However, it is recognized and must be remembered that: people’s differences in age-related cognitive decline form a continuum, not entirely discrete groups (of course, defining into groups is needed for treatment decisions); diagnostic criteria for Mild Cognitive Impairment (and its alternative terms) and dementia change, and so the points on the continuum that are deemed pathological or not can change; people’s cognitive level in old age

depends to a large extent on their prior intelligence and that is not always taken into account in reckoning whether a given level of cognitive function in old age represents a decline—in absolute terms, or relative to their age cohort—for that person; the same measured level of cognitive ability in old age can occur in the presence of very different levels of brain pathology (e.g. Alzheimer-type); and even people with no apparent cognitive decline can have Alzheimer-type pathology in their brains. In summary, studies that purport to describe contributions to non-pathological cognitive ageing must be examined with these caveats, and bearing in mind the possibility that some people in such studies might be in the early, undiagnosed stages of pathological cognitive impairment.

If the first warning about studies in non-pathological cognitive ageing is that the subjects in such studies will not invariably be non-pathological, the second warning is that apparent causes of cognitive ageing will not always be causes at all. It is quite common to read a report in which a variable is associated significantly with a cognitive test score in old age. Typically, the study is cross-sectional. Typically, too, the suggestion is made that the variable is a possible cause of cognitive differences in old age, of cognitive decline perhaps. It might be. But there are other possibilities. The follow-up studies of the Scottish Mental Surveys,⁷ for example, have shown that intelligence test scores from childhood are associated with health variables and health risk factors in middle and old age. Therefore, the cross-sectional ‘variable X versus cognitive ability scores’ finding in old age might—in part or whole—be the result of reverse causation: intelligence traits from early life affect later health. Another possibility is that the cross-sectional correlation is caused by some third—confounding—variable or set of variables and that the correlation is spurious, being the result of some more basic factor(s) that affect both the apparent cause and effect. Therefore, discovering associations between putative causes of cognitive ageing and cognitive ability test scores are only the beginning. Ideally, they should be studied longitudinally and be the subject of mechanistic investigations.

The landscape of cognition and how it ages

There is little age-associated decline in some mental functions—such as verbal ability, some numerical abilities and general knowledge—but other mental capabilities decline from middle age onwards, or even earlier.^{8,9} The latter include aspects of memory, executive functions, processing speed and reasoning. All of these so-called ‘fluid’ mental abilities are important for carrying out everyday activities, living

independently and leading a fulfilling life. When one fluid mental domain declines others tend to do so also.¹⁰ Second, slowed speed of information processing appears to account for a substantial proportion of age-associated decline in all affected cognitive domains, and the slowing has begun by the 30s,¹¹ as has the age-associated decline in some other aspects of cognitive function.¹² Within the range defined by 'normal cognitive ageing'—i.e. in people who would not meet the criteria for dementia or any of the varieties of 'mild cognitive impairment'—people differ greatly in the degree to which their brains decline with age. Identifying the risk factors for, and mechanisms of, individual differences in age-associated cognitive decline is among the greatest challenges to improve the wellbeing of older people.

Here, we address some contributions—general medical, genetic, vascular, physiological, dietary and lifestyle—to non-pathological cognitive ageing. This is an especially important problem because it involves such large numbers of people compared with the dementias. The USA's NIH emphasized the importance of studying the processes of 'normal' and 'successful' cognitive ageing.⁵ We should state at the start that individual differences in cognitive ability in old age reflect two things: differences in prior cognitive ability and differences in the degree to which change (typically deterioration) has taken place. Of the many possible contributors to cognitive ability level in old age, none yet known approaches the effect size of mental ability measured in childhood. Even as late as age ~80, childhood intelligence contributes ~50% of the variance, or more, to cognitive ability in old age in people without dementia.⁷

Disease, health and normal cognitive ageing

Inasmuch as age is the major risk factor for dementing illnesses, such as Alzheimer's disease, there is a case for considering these as representing an extreme end of the spectrum of age-associated cognitive decline. However, the dementias are not only quantitatively different in the degree of cognitive decline, but also they are often qualitatively different in the pattern of decline across the various cognitive abilities. For example, Alzheimer's disease is characterized by marked impairment of episodic memory and frontotemporal dementia by impaired executive function. Moreover, people with dementia often exhibit changes in behaviour and other aspects of mental state as well as declines in performing activities of daily living. Having said this, in advanced old age, when dementia has a high prevalence, distinguishing between normative and non-normative ageing is not simple. Indeed, this difficulty has been recognized by introducing categories such as

mild/minimal cognitive impairment which have a position somewhere between normal cognitive ageing and dementia.

One problem in distinguishing between normative and non-normative cognitive ageing is that neuropathological changes of Alzheimer's disease are widespread in older peoples' brains. In the MRC Cognitive Function in Aging Study (CFAS), around one-third of participants without dementia had moderate or severe neuritic plaque scores at autopsy.¹³ Another challenge is the observation that risk factors for dementia also increase risk of normative cognitive decline (age, hypertension, diabetes, physical fitness and education).^{1,5-7} Mirroring the problems distinguishing normative and non-normative cognitive ageing is a similar set of challenges differentiating normal physical ageing from age-associated disease. Disease, as defined by diagnosis and excepting dementia, is a poor predictor of cognitive decline,¹⁴ whereas physiological markers of health status are significantly correlated among themselves and with cognitive ageing.¹⁵ This mirroring has suggested that physiological and cognitive functions decline together in old age and led to what is termed the 'common cause' theory of ageing. This theory hypothesizes that although there are individual measure-specific mechanisms leading to decline, a considerable proportion of decline is attributable to some core biological processes that deteriorate with ageing. Candidates for such core processes include oxidative stress, telomere attrition, hormonal dysregulation and immuno-senescence. Research on the relationship between physical and cognitive ageing has thus sought to measure biomarkers of these processes to establish which pathways are implicated.

Another problem has been recognized that impacts upon our understanding of the relationship between physical health and age-associated cognitive decline: several disease states thought to affect cognition adversely are more common in people with lower early life IQ, including childhood IQ.⁷ Since childhood IQ, itself, is a strong predictor of cognitive abilities in later life, the disease state may be acting as a marker of lower childhood IQ and this might explain in whole or in part any association with lower cognitive ability in old age. For example, lower childhood IQ is associated with elevated blood pressure in middle age even after adjustment for social class, smoking and other factors.¹⁶ High blood pressure is thought to lead to cognitive decline, but few studies that examine this relationship adjust for the contribution made by childhood IQ to cognition in later adult life. Hence age-associated cognitive decline is best considered in terms of a life-course perspective. What appears to be the effect of an illness state on cognitive ability in old age might in part be the reverse: the effect of early life cognition on the risk of developing the disease state.

Genetic contributions to cognitive ageing

Heritability studies—using data from twins and families with adopted children—have estimated that the heritability of general cognitive ability is ~50%, increasing from childhood to adulthood and into old age. Some studies have shown that heritability decreases in very old age, though the contribution of genes to cognitive ability remains above 50%. It is likely that there are genetic influences on both the life-long trait of intelligence and specifically on age-associated cognitive decline.^{17,18}

Candidate genes studies have looked for associations between variations in specific genes and age-associated cognitive decline. Candidate genes include those previously associated with cognitive ability, dementia, cardiovascular disease, oxidative stress and longevity.¹⁷ There have been a number of published associations between candidate genes and cognitive ageing, but the gene coding for apolipoprotein E (*APOE*), a risk factor for Alzheimer's disease, is one of the few to have been replicated in multiple studies.^{19,20} In people within the normal range of cognitive ageing, possessors of the E4 allele of the *APOE* gene perform slightly worse on general cognitive ability and on the specific domains of perceptual speed, episodic memory and executive functioning. The influence of specific variants in 10 genes—e.g. *BDNF*, *COMT*, *DISC1* and *PRNP*—that had been previously associated with cognitive ageing, cognitive ability, Alzheimer's disease and autism were recently examined, and there was no evidence that they were associated with cognitive ageing in a cohort of ~1000 Scots with cognitive ability test scores available from ages 11 and 70 years.²¹ There are several reasons why candidate gene studies have identified so few replicable associations with age-associated cognitive decline. First, the genetic variants so far identified each account for at most only a small percentage (1–2%) of the variance in cognitive ageing and, as most studies contain only hundreds of participants, they are often underpowered for detecting such effect sizes. Second, many of the studies have been performed on participants from different populations and it is possible that different genes are important in different populations. Third, not all studies have used participants of the same age range. It may be that different genes influence cognition at different ages, even within what is classified as old age. Finally, the major limitation of candidate genes studies is that they rely on our limited understanding of both the biology of cognitive ageing and the functions of the candidate genes. This is where genome-wide association studies will be more useful, allowing up to one million genetic variants (both single nucleotide polymorphisms and copy number variations) spread throughout the genome to be

Table 1 Types of genetic contributions to understanding non-pathological cognitive ageing.

Types of genetic studies	Targets	Example results	Future	References
Heritability studies	Genetic influences on cognitive ability studied using twin, adoption and family designs	Genetic contributions to intelligence variation are: 41% childhood; 55% adolescence; 66% in young adulthood; about 60% in old age	Determine source of heritability by searching for molecular genetic influences	14,48
Candidate gene studies	Genes for cognitive ageing sought among genetic influences on: cognitive ability; dementia and other neurodegenerative disorders; cardiovascular disease; oxidative stress; longevity etc.	Variants in the following genes reported as associated with differences in cognitive ageing: <i>APOE</i> , <i>BDNF</i> , <i>COMT</i> , <i>DISC1</i> , <i>PRNP</i>	<i>APOE</i> is well established; other genes have largely failed to replicate	15–17
Whole-genome association	Whole-genome analysis used to reveal common variants influencing cognitive ageing	<i>LRP1B</i> haplotypes associated with successful ageing without cognitive decline	Replication in larger samples; improved genome coverage; detailed cognitive testing	49

The gene names are as follows: *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-O-methyltransferase; *DISC1*, disrupted in schizophrenia 1; *PRNP*, prion protein; *LRP1B*, low-density lipoprotein-related protein 1B.

genotyped. They are not biased towards a particular gene or genes.²² Table 1 summarizes and exemplify genetic approaches to the study of non-pathological cognitive ageing.

Cardiovascular disease and cognitive ageing

A delicate relationship exists between the circulatory system and the brain which, if upset by vascular disease, may affect normal brain functioning.²³ Diverse neurological symptoms may follow either transient or permanent disruption of blood flow to the brain. Long-lasting sensorimotor and behavioural disabilities are frequently observed after acute ischaemic stroke caused by complications of large-artery atherosclerosis.²⁴ A single large or repeated brain infarcts increase the risk of cognitive impairment, hence the term multi-infarct dementia. Even without dementia, stroke patients tend to perform poorly on cognitive

tests compared with healthy, non-stroke controls. Depending on the criteria used, cognitive impairment may affect up to 70% of patients.²⁵ Deficits in multiple cognitive domains are frequently observed, including general mental status, abstract reasoning, attention and specific memory functions, but usually some improvement occurs with time following the stroke event. Different stroke characteristics, including lesion laterality, may also influence cognitive outcomes in these patients; for example, left-hemisphere stroke is consistently associated with general cognitive impairment.²⁴ Although focal neurobehavioural deficits are common after stroke, general mental functions which depend on the integrity of the entire brain may also be affected.

Symptomatic atherosclerotic disease in one arterial site may represent similar pathology in other arteries.²³ For example, stroke patients frequently have concomitant coronary heart disease (CHD). Even in the absence of stroke, CHD predisposes to cognitive impairment which, in addition to systemic atherosclerosis, may result from cerebral hypoperfusion due to impaired cardiac function or infarcts caused by cardio-genic emboli travelling to the brain.²³ Although few studies have examined cognitive deficits in patients with milder CHD syndromes—including angina—poorer mental status, memory and executive functions have been reported in survivors of acute myocardial infarction (AMI).²³ However, known CHD risk factors, which often cluster in individual patients, may independently influence cognition. When appropriately controlled for, AMI may no longer associate with cognitive performance.²⁶ In contrast, end-stage congestive heart failure is associated with deficits in executive function, memory, concentration and psychomotor speed.²³ Cardiac output, which may be severely reduced due to impaired ventricular function, predicts cognitive function in these patients, although as yet, it is unknown whether heart transplantation actually improves cognitive outcomes in patients with long-standing heart failure.

Similarly, patients with peripheral arterial disease (PAD) affecting the lower extremities commonly have atherosclerotic lesions in major arteries supplying the heart muscle and the brain. Deficits in psychomotor speed, problem solving and abstract reasoning are common in neurologically intact patients with very advanced PAD, such as leg amputees.²⁷ The extent of these deficits may differ only marginally from that seen following overt stroke. In these patients, disease severity may be an important predictor of cognitive function. In population-based studies, elderly people who experience leg pain while walking, the clinical hallmark of PAD, have been found to be at an increased risk of progressive cognitive decline, particularly in verbal memory, which is not explained by the influence of a previous stroke, depressed mood or concomitant vascular risk factors on cognition.²⁶

Inflammation and cognitive ageing

There is strong evidence linking markers of inflammation with atherosclerosis and cardiovascular disease, but its relationship with cognition is less well defined. Current prospective and cross-sectional studies provide conflicting views with positive and null findings being reported between late-life biomarker levels and cognitive ability.^{28,29} Of these studies, few have assessed a large cohort of subjects over a long-term follow-up using an extensive battery of cognitive tests.

In terms of the inflammatory biomarkers studied, there is a reasonably large body of work on the downstream acute-phase protein C-reactive protein (CRP), and the upstream cytokines tumour necrosis factor alpha and interleukin-6. The magnitude of the effect sizes between these markers and cognition is typically small, with the biomarkers explaining ~1% of the variance of the cognitive test scores. In addition to inflammatory biomarkers, some studies have also integrated rheological and thrombotic factors, such as plasma viscosity and fibrinogen into their analyses. Initial findings for these markers are again mixed, although a causal rheology-cognition association is certainly plausible via a 'sticky blood' hypothesis. Explicitly, some suggest that increased blood viscosity has an effect on cerebral blood flow at a microvascular level.³⁰

One study showed associations between both CRP and fibrinogen with cognitive ability at age 70 years.³¹ However, upon adjustment for a measure of IQ at age 11, the associations were markedly attenuated. Further, the age-11 IQ scores also predicted age-70 CRP levels. This again raises the possibility of a reverse causation argument, in which lower childhood IQ leads to more inflammation in later life. Longitudinal data such as these are clearly a desirable study feature, although investigators might also consider the inclusion of a vocabulary-based test to estimate peak prior cognitive function. Measures such as the National Adult Reading Test are fairly robust estimates with scores on vocabulary-based tests showing little evidence of change over time.³²

Given the high variability and acute nature of some inflammatory biomarker levels in old age, especially CRP, it may be relevant to use genetic variants as predictors of lifetime exposure to inflammation. Such an approach treats the intermediate phenotype (the biomarker level, such as CRP) as a biased measure. Instead, it models directly a gene-cognition association using genetic information, such as single nucleotide polymorphisms. Because genetic variants are determined at conception, they are less likely to be affected by confounding. Therefore, the use of such variants as predictors may be an approach

that will help to elucidate causal mechanisms. A caveat with this approach is the very large sample size required to detect significant associations. It may be that collaborative work with replication across different populations is required to reduce the possibility of false-positive findings and to ensure adequate power to detect what are almost certain to be small associations.

Neurobiology and cognitive ageing

The brain undergoes pronounced age-associated structural changes in old age. The most obvious is a steady decrease in brain size, balanced by an increase in ventricular spaces and cerebrospinal fluid. Brain atrophy accelerates in old age and shows an anterior–posterior gradient, with the most severe effects occurring in prefrontal regions.³³ Compared with overall brain, age-associated shrinkage is much smaller in the cerebral parenchyma. In the latter, atrophy starts much earlier in life and is more steady in grey matter (the neuron cell bodies) and cortical thickness than in white matter (the nerve fibres connecting different brain areas). Brain white matter volume tends to be relatively stable in healthy adults until about age 70, when steep decline, with an even more pronounced anterior–posterior gradient, can set in.^{8,33,34} Also, cerebral dopamine receptor density depletes with age, which plays a central role in regulating attention and in modulating response to contextual stimuli.⁸ A variety of mechanisms are likely to be causal in the normative age-associated decline in brain structure, including hypertension, age-associated vascular and microvascular changes, oxidative stress, recurrent inflammation and stress-related corticosteroid levels.^{33,35}

It has been proposed that the loss of white matter integrity is an especially critical factor in normal cognitive ageing, since it leads to impaired information transfer between different cortical areas, from a loss of transfer speed in the case of demyelination to complete disconnection when axonal disruptions occur. Interactions between distant cortical areas are considered as crucial for the emergence of higher cognitive functions.³⁴ Until recently, problems with white matter integrity could mainly be detected as lesions that appear as hyperintensive patches on structural magnetic resonance imaging (MRI) scans and were mostly quantified using visual rating scales. Even though this procedure is laden with various measurement issues, small but consistent relationships with higher cognitive functions have been detected this way.³⁶ The advent of various new neuroimaging techniques, most notably diffusion tensor MRI, now allow for a much more detailed look at microstructural changes in cerebral white matter, including

fibre tract-specific assessments of white matter integrity (quantitative tractography).³⁴ However, despite these technological advances, the studies to date report associations between structural brain differences and cognitive ability measures in old age that tend to be modest in size and sometimes elusive.^{8,33,34}

Two major explanations have been brought forward for this rather surprising pattern of results. First of all, people are assumed to differ in their cognitive reserves, which can be defined as the brain's capacity to buffer the effects of insults. The main determinants of cognitive reserve are early life cognitive ability (the 'baseline'), education level and occupational complexity, with the former being a strong predictor of the latter two.^{12,35} Second, it is assumed that the ageing brain compensates structural losses in functional areas by recruiting previously unrelated parts of the brain (preferably in the prefrontal cortex and in corresponding contra-hemispheric areas) to take over the role in cognitive functions.^{8,34} Both accounts have received some empirical support,^{8,34,35} so they might explain why normative age-associated structural brain changes do not inevitably lead to cognitive decline.

Diet, lifestyle and cognitive ageing

The role of diet and other lifestyle factors in successful brain ageing has been attracting increasing scientific and public interest. Recent findings suggest that improving the diet of older people might help to delay the onset, or slow the progression, of age-associated cognitive decline. Current research has focused on the role of specific dietary elements and dietary patterns.

Some research supports the importance of a diet rich in B-vitamins, antioxidants and omega-3s for mental fitness. B-vitamins are essential for maintaining normal brain function and memory. Epidemiologic data suggest a protective role for B vitamins, particularly vitamin B12, B6 and folate (B9) on cognitive function. Moreover, B-vitamins help to regulate homocysteine levels, which is a risk factor for cognitive decline.³⁷ Oxidative damage has been implicated in ageing and age-associated cognitive decline. Dietary antioxidants (such as vitamins C, E, beta-carotene and flavonoids) found in fruits and vegetables may help protect against oxidative damage by boosting antioxidant defences. Evidence from cross-sectional studies supports a link between antioxidant status and cognitive function in older people.³⁸ In addition to antioxidant vitamins, fruits (such as blueberries) and vegetables contain plant polyphenols—compounds thought to interact with ageing neurons, increasing their capacity to maintain proper functioning during ageing.³⁹ Omega-3 fatty acids (particularly DHA) are

highly concentrated in the brain and the habitual consumption in later life of oily fish, rich in omega-3s, is associated with a reduced risk for cognitive decline and dementia.^{37,40} They have been found to have anti-inflammatory, antioxidant and neuro-protective properties. Experimental evidence supporting a cognitive benefit to micronutrient supplementation in old age has been inconclusive. However, nutritional intake is based on a complex interaction of both macro- (proteins, fats, carbohydrates) and micronutrients (vitamins, minerals). For that reason, some researchers have directed their attention to the effects of dietary patterns. Prevailing scientific opinion points to a pattern of intake reflected in a 'Mediterranean diet'—rich in vegetables, legumes, fruit, nuts, cereals, fish and moderate amounts of alcohol (particularly red wine) and low in meat, poultry and dairy products—to maximize one's cognitive abilities into old age. Conversely, a diet high in refined sugars, cholesterol and trans-fats might be associated with poorer cognitive outcomes in older adults.³⁷ The interaction between genes and nutrition in recent research highlights the interplay between internal and external environments. Cognitive benefits were found in older adults consuming omega-3 fatty acids but only in non-APOE e4 carriers.⁴¹ This finding supports the concept of an individual response to dietary intake and heterogeneity in cognitive ageing.

In conjunction with diet, other lifestyle factors such as smoking, drinking, physical activity and sleep influence cognitive ageing.^{6,12} Evidence is growing that moderate levels of alcohol intake in older people can be beneficial; they are associated with better cognitive performance than either abstinence or heavy drinking and may have a protective effect against dementia and cognitive decline.⁴² This risk reduction is partly attributable to the protective effects of alcohol on cardiovascular and cerebrovascular health. Smoking, primarily via detrimental effects on vascular disease, is a significant risk factor for cognitive impairment. A dose-response effect is evident for the number of cigarettes smoked during the lifetime and the degree of cognitive decline.⁴³ Giving up smoking at any age may prevent further smoking induced cognitive harm.

Future research should consider the full impact of socio-demographic factors; education, for example, is known to shape food choices in adulthood and therefore plays an important confounding role in the relationship between diet and cognition. Although further investigation is needed to clarify whether specific nutrients help to protect the brain from damage and counteract the effects of ageing, human epidemiologic studies provide some supporting evidence that a diet rich in plant matter and fish could offer protection against cognitive decline.

Active lifestyle and cognitive ageing

When considering potential determinants of age-associated cognitive decline, engaged and active lifestyles are often reported as protective.⁴⁴ This may be of particular interest to clinicians and indeed the public more generally, as it presents opportunities for delivered interventions or purposeful changes to habits intended to reduce cognitive decline. A recent UK Government review incorporated research linking physical activity or exercise and cognitive function, the consensus being that age-associated cognitive decline is apparently delayed or reduced in more physically active individuals.⁶ An important caveat to this is that the physical activity need not be strenuous; individuals who walk more may experience less decline in later life.^{6,44} Further investigation is warranted, particularly to examine whether there are critical periods across the life-span when physical activity needs to be initiated and maintained and what type of physical activity (e.g. aerobic versus anaerobic) might confer the greatest benefits.⁶ Not all studies report an exercise-cognitive decline association, perhaps due to variability in the physical activity measurements, the validity of the cognitive assessments and length of follow-up in old age, and the timing and duration of the physical activity itself.⁴⁴ That said, there are a number of mechanistic hypotheses which could account for an association between increased physical activity and reduced cognitive decline. Most notably, cardiovascular risk and disease profiles are known to play a role in the trajectory of cognitive decline in later life; physical activity lowers these risk factors.^{5,6,44}

Participation in activities of a mental or intellectually stimulating nature has also been shown to predict reduced cognitive decline. In this domain, the notion of ‘use it or lose it’ is proposed: the continued deployment of cognitive abilities through activities requiring cognitive effort may have direct effects on the brain, in terms of structure and/or function.^{44,45} This is closely linked to the ‘cognitive reserve’ hypothesis. Individuals who are more cognitively active or engaged may accrue greater ‘reserve capacity’ across the lifecourse, and subsequently delay the onset of age-associated cognitive decline or reduce the impact of this.^{6,35} However, any association found between mentally stimulating activities and cognitive decline must be clearly shown to be independent of premorbid cognitive function.⁴⁶ That is, the association must not be driven by the fact the higher ability individuals are more likely to be cognitively active throughout life and into old age (not just in terms of leisure but occupationally also); another example of possible reverse causation. The presumed protective effect may be due to the high degree of stability in cognitive function across the lifespan and not from participation in the activities themselves. To examine if there is

Table 2 Some other potential contributors to non-pathological cognitive ageing.

Potential contributor	Details
Self-reported health status	Individuals reporting poorer health status experience greater cognitive decline. Likely mechanisms would implicate increased burden of cardiovascular disease and its risk factors, increased levels of inflammatory and oxidative stress markers etc. (see below)
Cardiovascular disease and its risk factors	Normal cognitive functioning affected by vascular disease, e.g. by disruption of blood supply to the brain after stroke, or atherosclerotic lesions in major arteries. Risk factors including high blood pressure also associated with poorer cognitive function, although caution needed as earlier cognitive ability itself may be predictive of the presence/severity of risk factors in later life, an example of possible reverse causation
Physiological markers of health status	Associations between physiological markers of health (including inflammation, oxidative stress etc.) and cognitive decline are often discussed in terms of the common cause hypothesis: this suggests there may be shared biological processes of decline across domains of physical and cognitive health. It is necessary to identify biomarkers of decline processes to elucidate potential pathways. Markers of inflammation (i.e. CRP, IL-6, TNF- α) are linked to cardiovascular disease and atherosclerosis, but associations with cognitive decline are in need of further study. There are indications that levels of some markers in old age may be predicted by earlier cognitive function; possible reverse causation
Diet and nutrition	Some research links diets higher in B-vitamins, antioxidants and omega-3s with higher cognitive function. Mechanisms for association could include regulation of homocysteine or oxidative stress pathways; however, experimental studies are inconclusive. 'Mediterranean diet' is thought to be protective—with the presence of vegetables, fish and moderate alcohol
Smoking and alcohol	Smoking increases the risk of vascular disease and thus has been linked to poorer cognitive health; moderate alcohol consumption appears to be, if anything, beneficial
Activity participation and physical fitness	Active and engaged lifestyles seen as beneficial for later cognitive function, with particular emphasis on physical activity, which may reduce likelihood of CVD or related conditions, and also association between measures of physical fitness and cognition, again thought to be part of 'common cause' hypothesis of ageing. Mental engagement is often promoted as one of the key ingredients for successful cognitive ageing; however, there are large potential confounds in terms of participation in these activities and earlier level of cognitive ability. Suggested mechanisms often cite direct effects of mental stimulation on brain structure and function
Education and social class	More years spent in formal education and higher social class are associated with less cognitive decline. Mechanisms could include increased 'cognitive reserve' through educational and occupational trajectories, safer working and living environments, access to better health care etc. Both factors are highly correlated, and likely to be partly predicted by earlier cognitive level

truly a protective effect, more studies are needed which are able to control for an early measure of premorbid cognitive function.

The reason such activities are of particular interest derives from the fact that they may suggest simple, cost-effective lifestyle interventions

to ameliorate or delay age-associated cognitive decline. To date, however, cognitive intervention trials have not produced robust, replicable benefits. A recent review including 10 randomized control trials reported a mean effect size of 0.16 across a range of interventions, although the authors noted that most studies failed to include matched, active controls or placebos and that the benefit of the intervention often failed to generalize across varied cognitive outcomes.⁴⁷ Few studies included a lengthy follow-up to determine whether any apparent short-term gains in cognitive test performance were reflected at a more distal time point. This area will benefit from increased scrutiny and well-designed trials. Furthermore, it should be remembered that any beneficial interventions suggested need the compliance of those at risk in real world settings, as with other forms of medical treatment or medication use. Such behaviours are confounded by the ability to seek out and comprehend the information provided.

Conclusion

The interest in cognitive ageing is as understandable as it is compelling, for personal, scientific and practical interest. Personally, as we become aware of cognitive processes deteriorating, we witness the diminishing of something at the core of our rational self. Scientifically, it is a fascinating problem, namely to construct the multivariate recipe for successful cognitive ageing (a summary of the current review is provided in Table 2). Practically, demographic changes mean that our care services and economies will be better placed to cope with the increasing burden of cognitive ageing if there are clues to amelioration and prevention. Some contributions to cognitive ageing are clearly more open to intervention than others: smoking, exercise, and diet can be changed following advice. Mechanistically, even the contributions from genetics and from childhood intelligence should not be looked on too pessimistically; even these factors have mechanisms which might afford interventions.

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Childhood IQ and in-service mortality in Scottish Army personnel during World War II

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ABSTRACT

The Scottish Mental Survey of 1932 (SMS1932) provides a record of intelligence test scores for almost a complete year-of-birth group of children born in 1921. By linking UK Army personnel records, the Scottish National War Memorial data, and the SMS1932 dataset it was possible to examine the effect of childhood intelligence scores on wartime military service mortality in males. There were 491 matches between World War II (WWII) Scottish Army fatalities and the SMS1932 database; 470 (96%) had an age 11 mental ability score recorded. The mean (S.D.) age 11 IQ score of those who died on active service in WWII was 100.78 (15.56), compared with 97.42 (14.87) for male Army survivors ($p < 0.0001$; Cohen's $d = 0.22$). Men who took part in the SMS1932 and who were not found in the Army database had a higher mean score (100.45, S.D. = 14.97) than those men who had been in the Army, regardless of whether they died or survived (mean IQ = 97.66, S.D. = 14.94; $p < 0.0001$; Cohen's $d = 0.19$). Male soldiers with a higher childhood IQ had a slightly increased risk of dying during active service in WWII. Men who did not join the Army had a higher IQ than men who did. Further research in this area should consider naval and air force personnel records in order to examine more fully the complex relationship between IQ and survival expectancy during active service in WWII.

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1. Introduction

People with higher intelligence test scores tend to live longer. The first peer-reviewed report of the association between mental ability and mortality was among a sample of Australian Vietnam war veterans who took mental tests when they joined the armed services and were followed up for survival data after war service was completed (O'Toole & Stankov, 1992). The intelligence–mortality association is now well replicated among studies in which IQ-type data were collected in youth, prior to any likely onset of illness that could affect both the test scores and subsequent health (Batty, Deary, & Gottfredson, 2007; Hart, Taylor et al., 2003; Whalley & Deary, 2001). There is, however, an interesting exception to this 'lower intelligence–higher mortality risk' association.

In one locality, Scottish men with higher childhood IQ scores were more likely to die on active service during World War II (WWII). In their investigation into the effects of childhood IQ and survival up to age 76 in the Aberdeen-based participants of the Scottish Mental Survey 1932 (SMS1932; Scottish Council for Research in Education [SCRE], 1933), Whalley and Deary (2001) found that the influence of age 11 IQ on survival to old age was weaker in men than in women. They attributed this to the effect of WWII on death rates in men. Whereas women with a high childhood IQ had a consistently better average survival expectancy than women with a low childhood IQ, the pattern for men was different. Whalley and Deary observed that "for men with a high IQ, survival suddenly drops during the Second World War and does not catch up and improve on that in men with a low childhood IQ until later in life" (p. 820). This suggested that the men who were killed during active service in the WWII may have had a relatively high IQ.

The present study follows up this suggestion. The age of people in the SMS1932 was such that many of the males

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would later join the armed services during hostilities in WWII. Here, we bring together data from: the Scottish Mental Survey 1932 (which comprises mental ability scores on the same valid mental test for nearly all children born in 1921 and attending schools in Scotland on June 1st 1932); United Kingdom Army records (which includes all WWII personnel); and the Scottish National War Memorial (which records Scottish deaths in the armed services). WWII military test data were not available to the authors. The present data-linking exercise provides an opportunity to study the association between childhood (age 10.5 to 11.5 years) intelligence in the SMS1932 and the survival of male Army personnel during WWII. Childhood IQ from the SMS1932 is a highly reliable indicator of adult IQ, evidenced by the stability of IQ across the lifespan from age 11 to almost age 80 years (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman, Starr, Whalley, & Fox, 2004). The aims of this study are: (1) to extend the scope of Whalley and Deary's (2001) previous work in the small Aberdeen subsample of the SMS1932 to include the entire SMS1932 dataset in examining whether a relation exists between childhood mental ability and survival expectancy in male soldiers during WWII; and (2) to examine any differences in childhood mental ability between those who were enlisted in the Army in WWII and those who were not.

2. Method

2.1. Participants and datasets

The present study involved the linking of four large datasets—two Scottish, one UK-wide, and one that applies to the British Commonwealth—which are described below. The first three are the 'principal' datasets used in the study.

2.1.1. Scottish mental survey 1932 (SMS1932)

The present study's reference population is the participants in the Scottish Mental Survey of 1932, conducted by The Scottish Council for Research in Education (SCRE, 1933). This exercise tested the mental ability of almost all Scottish children born in 1921 and attending school on June 1st 1932. The original objectives of the study were: a) to quantify the rates of mental deficiency; and b) to obtain information about the distribution of intelligence throughout the country. A group-administered general mental test was given—a version of the Moray House Test No. 12, referred to here as the MHT. It comprised 71 verbal reasoning (predominantly), numerical, spatial and other items and with a maximum score of 76. The correlation between the MHT and the Stanford-Binet Intelligence Test was 0.81 for boys and 0.78 for girls (SCRE, 1933). There are some currently-missing ledgers for the areas of Fife, Wigtownshire and Angus. The computerised SMS1932 dataset consists of 86,520 entries (43,569 males). One region tested a small sample of children born in 1922 and 1923, in addition to 1921, but for the purposes of this study the SMS1932 dataset we refer to contains the male entries only, born in 1921 ($N = 42,605$).

2.1.2. Army inventory

An electronic index of archived Army personnel records obtained from the United Kingdom's Army Personnel Centre

(Kentigern House, Glasgow, Scotland) contains listings for 8,009,328 men and women who served in the Army after 1921 and no longer have any reserve liability. 208,388 entries in this database have 1921 birthdates. Each entry includes Army service number, name (surname and initials), date of birth, and regiment. Many of the records are incomplete.

2.1.3. Scottish National War Memorial records (SNWM)

The Scottish National War Memorial—based in Edinburgh Castle in Scotland—has archived records of the WWII Rolls of Honour, documenting Scots who died during active service in the armed forces. We obtained permission to access the electronic index—which will be referred to as SNWM—containing listings for 57,705 WWII deaths. Information includes Army service number, name, regiment, rank, date of death, and place of death. Date of birth information is not included.

2.1.4. Commonwealth War Graves Commission

The 'Debt of Honour Register' is the Commission's database listing the 1.7 million men and women of the Commonwealth forces who died during the two world wars. The register, available at www.cwgc.org, can be searched for personal, service and commemoration details of war casualties, on an individual basis. This database is useful for verifying details of casualties and providing date of death, rank and regimental information, where missing in other Army datasets.

2.2. Procedure

Table 1 shows the variables available for matching in each of the three principal datasets. All matching was carried out without knowledge of MHT (childhood mental ability) scores. Although the SNWM database contains most of the relevant Army information for the purposes of this study, date of birth information is missing. Date of birth is necessary to enable the cross-matching of military records with the SMS1932 at a later stage. Prior experience in matching the SMS1932 to databases in Scotland indicates that, with surname, initials and date of birth available, ambiguity in matching is minimal (Hart, Deary et al., 2003). The SNWM dataset ($N = 57,705$) was compared with the Army Inventory database ($N = 8,009,328$) in order to identify records which matched, and to provide date of birth information for as many people in the SNWM index as possible.

Table 1
Variables available for matching in each of the datasets

	Army ^a	SNWM ^b	SMS1932 ^c
Army service number	✓	✓	
Name	✓	✓	✓
Date of birth	✓		✓
Regiment	✓	✓	
Rank		✓	
Date of death		✓	
Place of death		✓	
MHT score			✓

^a Army Inventory.

^b Scottish National War Memorial.

^c Scottish Mental Survey 1932.

We matched records using Army service number (where possible), given that this is a unique identifier for each individual. A positive match was made if the Army service number in both datasets (Army Inventory and SNWM) was identical and the surname and initials matched (e.g. Anderson JJP) or partially matched (e.g. Anderson JJ and Anderson JJPQ). In the absence of a service number, a match was made if surname and initials were identical or partially matched (as above). Where matching relies on name only, there is less certainty about the accuracy of these matches. However, over 79% of matches were made using the Army service number. A total of 25,740 matches were made between the Army Inventory and SNWM, of which 1514 had dates of birth in 1921 and potentially took part in the SMS1932 at age 11.

These 1514 people were then cross-matched with the SMS1932 male dataset ($N=42,605$) in order to determine their age 11 MHT (mental ability) scores. Exact matches using surname, forename and date of birth were found for 401 men. Of the remaining 1113 cases, 473 were excluded from further consideration at this point, as follows. First, 94 were women. Second, since place of birth data were available, 346 men were excluded on the basis that they were born in England and therefore unlikely to have attended school in Scotland at age 11 and participated in the SMS1932. Third, men with a Fife, Wigtownshire or Angus birthplace were also excluded ($n=33$) as the SMS records for these counties are missing. The remaining 640 unmatched cases were manually checked against the SMS1932 dataset to obtain as many further matches as possible. Decisions on hand matching were made using all the available information, including name, date of birth, school location, and county of residence at age 11 (in 1932).¹ Hand matching produced a further 90 matches, bringing the total number of war death matches born in 1921 (and who participated in the SMS1932) to 491.

In an attempt to identify Scottish soldiers who took part in the SMS1932 but were not killed during WWII (presumptive SMS1932 war survivors), we completed a final data matching stage. At this stage, 42,648 entries referring to female Army personnel were identified (where the Army service number is prefixed with a W) and excluded from the Army dataset. The amended Army Inventory, consisting of 165,740 males born in 1921, was cross-matched (using name and date of birth variables) with the SMS1932 male database ($N=42,605$) generating automatic 'in Army' matches. Among the 6838 positive matches are men with an Army entry, regardless of whether or not they survived the war.

The 'in Army' group ($N=6838$) consists of 491 war deaths and 6347 'presumptive SMS1932 war survivors'. These 'presumptive war survivors' are compared, in terms of age 11 IQ, to the 491 possible war deaths from the SNWM (SMS1932 war dead). The 'in Army' group on which the

Table 2Descriptive data for the SMS1932^a men and army status matches

	Total cases	Valid IQ score	Mean IQ score	S.D.
WWII dead	491	470	100.78	15.56
Presumptive WWII survivors	6347	5994	97.42	14.87
'In Army'	6838	6464	97.66	14.94
'Not in Army'	35,767	33,635	100.45	14.97

^a Scottish Mental Survey 1932.

analyses are based comprises those cases with a valid age 11 MHT score ($N=6464$). The remaining 35,767 cases in the SMS1932 dataset are considered to be 'not in Army', of which 33,659 have childhood ability scores.

Using the Commonwealth War Graves Commission website, we hand searched the 'Debt of Honour' listings of UK war dead, for each of the 491 'war death' matches, in order to complete any missing date of death, rank and regimental information. We categorised the 'war deaths' into four groups according to skill and rank: 'less skilled' other ranks (private, rifleman, driver, fusilier, gunner, drummer); 'more skilled' other ranks (craftsman, sapper, signalman, trooper); 'non-commissioned officers' (bombardier, corporal, lance bombardier, lance corporal, lance sergeant, sergeant, staff sergeant); 'officers' (2nd Lieutenant, Lieutenant, Captain, Major).

3. Results

Of the 491 cases we identified during the matching process to be 'war deaths', 470 (96%) had valid age 11 MHT scores. 21 cases have no MHT score. The MHT scores were corrected for age by performing a regression analysis. The standardised residuals were then converted to standard IQ-type scores, with mean = 100 and S.D. = 15 (Table 2). The mean IQ (S.D.) score of the male WWII 'war deaths' who took part in the SMS1932 is 100.78 (15.56), and the mean IQ of those identified as being in the Army but not in the SNWM (presumptive survivors) is 97.42 (14.87): $t(df=6462)=4.70$, $p<0.0001$, Cohen's $d=0.22$. Of the 'not in Army' group, 24 have an incomplete date of birth listed. Therefore, analyses are based on 33,635 males. These men who took part in the SMS1932 and could not be found in the Army Inventory had higher mean IQ scores (100.45, S.D.=14.97) than those who had been enlisted in the Army (97.66, S.D.=14.94): $t(df=40,097)=13.704$, $p<0.001$, Cohen's $d=0.19$.

The mean IQ for the four categories of soldier in the 491 'war death' matches was as follows. The 'less skilled' other ranks (60% of 'war deaths') had a mean IQ (S.D.) of 95.33 (14.78). The 'more skilled' other ranks (13% of 'war deaths') had a mean IQ (S.D.) of 105.41 (12.52). The 'non-commissioned officers' (20% of 'war deaths') had a mean IQ (S.D.) of 106.7 (12.06). The 'officers' (7% of 'war deaths') had a mean IQ (S.D.) of 121.89 (6.03).

4. Discussion

This investigation aimed to link the Scottish Mental Survey data of 1932 with United Kingdom Army service records and Scottish WWII death records in an attempt to replicate and explain the dip in survival rates of high IQ men during the

¹ There were many entries in the SMS1932 dataset with misspellings or abbreviations of names (e.g., Wm for William, Alex for Alexander) and in many cases the date of birth differed very slightly between the two datasets. Database anomalies such as these prevented an otherwise-obvious exact match from being made in the previous computerised stage. A match was accepted if all other information was identical. If there was any doubt, especially where a common name occurred (e.g., if there were two John Smiths who went to the same school in the same area and had slightly different dates of birth) no match was made.

WWII (Whalley & Deary, 2001). We found that men killed on active service in the Army during WWII had a slightly higher childhood IQ score than soldiers who survived. This partially supports, in a nationwide analysis, previous findings from the Aberdeen subsample of an association between higher childhood IQ and an increased risk of dying in WWII. Whalley and Deary (2001) suggested that part of this anomaly in the survival rates of the higher IQ men may be a result of some men being rejected from active service because of low mental ability. However, the present study would argue against this, given that the mean age 11 IQ score of men who could not be found in the Army database is higher than those who could. One possible explanation for this trend is that the higher ability men may have volunteered for (or been conscripted into) the Royal Air Force (RAF) or Royal Navy. These services had smaller manpower requirements than the Army and were thus able to take what seemed to them the 'best material' (Ungerson, 1953). Another possible explanation could lie in the fact that key personnel in war industry and the civil defence services were exempt from military service under the Schedule of Reserved Occupations (Ministry of Labour and National Service, 1947).

The overwhelming majority of the war deaths, as might be expected, occurred during 1942–1945. This was a period when the Army was engaged in heavy fighting in the Middle East, Italy and north-west Europe. But why was the mean IQ of the dead soldiers higher than those who survived? Although the majority of war deaths in this study (60%) belong to the 'less skilled' other ranks, who have a lower mean IQ score (95.33) than the 'presumptive survivors' (97.42), the IQ of the war dead is inflated by the minority of 'more skilled' other ranks, NCOs and officers. This seems to be partly a result of the increasingly technological nature of warfare which meant that more skilled soldiers were required on the frontline. In this respect, troops in the more technical arms, such as the Royal Armoured Corps, the Royal Engineers, and the Royal Corps of Signals, make up 13% of the war deaths in this study, but have a mean IQ score of 105.4. It also seems to be partly related to military rank. Officers and NCOs, who comprise 27% of the fatalities and have respective mean IQ scores of 106.7 and 121.89, were expected to fulfil leadership roles and thus would have been more likely to expose themselves to greater risk. Furthermore, there might be some link to the well-documented relationship between mental ability test scores and job performance (Schmidt & Hunter, 1998). It is possible that, in general, higher IQ soldiers displayed greater combat motivation and therefore put themselves in more life threatening situations.

To our knowledge, this has been the first attempt to link together childhood mental ability scores and war records. It is an important exercise because war fatalities appear to be a notable exception to the general finding that higher IQs are associated with lower risks of death. However, the large databases linked here proved demanding to match. Most of the matches achieved during the merging processes were exact. Many others were extremely close, involving the use of an abbreviated forename, misspelling or slight error in the date of birth when all other information was identical. Furthermore, there are some limitations to this study. The computerised Army Inventory has many missing data and duplicate entries with incorrect service numbers, causing

significant problems throughout the matching process. Each entry was listed by surname and initial(s), whereas the other two datasets we used had more complete name information including forenames. Had this information been available, it is likely that a higher number of matches could have been made and with more confidence.

Each stage of matching introduced error, and the possibility of bias must be considered. Some of the matching was done by hand. Although we can be confident that this manual process was accurate, in terms of finding unique matches, it is possible that there were a very small number of false positives and negatives. Possible matches containing names with common forenames and surnames were more likely to be rejected than those with more unusual names: the likelihood of there being two people with an unusual first or last name, at school in the same area and with an identical date of birth is decreased. It should be noted again, however, that records were matched, at each stage, in the absence of MHT scores. Matching in this blind manner reduces the possibility of observer bias.

At each stage, we allocated individuals from the datasets into groups according to their Army or survival status. But these allocations are only as good as our method for matching, based on the information available to us. For example, once the 'in Army' matches have been identified, the remaining non-matches are labelled 'not in Army'. However, the non-matches are just that; failure to achieve a match between the two datasets does not necessarily preclude them from ever having been in the Army.

As far as the relationship between IQ and risk of dying in any sphere of life is concerned, there are often difficulties in separating the effects of IQ on mortality from the potential confounding effects of social factors (such as socioeconomic background) to which IQ is related. The present study, however, is limited to the information included in the three principal datasets.

This study examined the link between in-service mortality and childhood mental ability scores in Army personnel only. A number of the men who took part in the SMS1932 would have joined the Royal Air Force or Royal Navy. Any association between IQ and Royal Navy or Royal Air Force fatalities remains to be considered. Therefore, further research in this area could consider Navy and Air Force personnel records as well as the roles occupied by those higher IQ individuals in order to examine more fully the complex relationship between IQ and survival expectancy during active war service.

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Dietary factors and biomarkers of systemic inflammation in older people: the Lothian Birth Cohort 1936

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Abstract

Epidemiological studies have reported inverse associations between various single healthy diet indices and lower levels of systemic inflammation, but rarely are they examined in the same sample. The aim of the present study was to investigate the potential relationships between biomarkers of systemic inflammation (C-reactive protein (CRP) and fibrinogen) and overall foods (dietary patterns), single foods (fruits and vegetables), and specific nutritive (antioxidants) and non-nutritive (flavonoids) food components in the same narrow-age cohort of older adults. The dietary intake of 792 participants aged 70 years from the Lothian Birth Cohort 1936 was assessed using a 168-item FFQ. Models were adjusted for age, sex, childhood cognitive ability, lifestyle factors and history of disease. Using logistic regression analyses, CRP (normal *v.* elevated) was favourably associated (at $P < 0.05$) with the 'health-aware' (low-fat) dietary pattern (unstandardised $\beta = (0.200, \text{OR } 0.82, 95\% \text{ CI } 0.68, 0.99)$ and fruit intake (unstandardised $\beta = (0.100, \text{OR } 0.91, 95\% \text{ CI } 0.82, 0.99)$), including flavonoid-rich apples (unstandardised $\beta = (0.456, \text{OR } 0.63, 95\% \text{ CI } 0.439, 0.946)$). Using linear regression analyses, fibrinogen (continuous) was inversely associated (at $P < 0.05$) with the Mediterranean dietary pattern (standardised $\beta = (0.100)$, fruit intake (standardised $\beta = (0.083)$, and combined fruit and vegetable intake (standardised $\beta = (0.084)$). We observed no association between food components (antioxidant nutrients or specific flavonoid subclasses) and inflammatory markers. In the present cross-sectional study, nutrient-dense dietary patterns were associated with lower levels of systemic inflammation in older people. The results are consistent with dietary guidelines that promote a balanced diet based on a variety of plant-based foods.

Key words: Dietary patterns: Inflammation: FFQ: Cognitive ability

Chronic low-grade inflammation has been implicated in the pathways of numerous diseases^(1,2). Elevated plasma levels of systemic inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen have been shown to predict CVD⁽³⁾, stroke, type 2 diabetes mellitus, cancer and dementia^(4,5). Dietary intake has long been known to play a role in the physiological response to inflammation. Therefore, nutrition may influence the development and progression of inflammatory conditions and may be useful in their prevention and treatment at a population level⁽¹⁾. Dietary intake in relation to low-grade inflammation has been investigated in a number of ways. One approach, based on the overall diet, takes account of trends among food components, represented in dietary patterns. Findings from population studies^(6–8) and

intervention trials⁽⁹⁾ provide evidence that a Mediterranean dietary pattern may be particularly beneficial in reducing inflammation. Recent prospective studies have confirmed that adherence to a healthy diet over time reduces the risk of long-term inflammation^(10–13). A second approach, which examines the role of single foods, has suggested that fruits, vegetables and whole grains are associated with lower concentrations of CRP^(6,11,14–20) and fibrinogen^(7,21–25). A third strand of research has focused on specific nutrient and non-nutrient components of foods. Dietary antioxidants such as β -carotene, Zn, Se, vitamin C and vitamin E have been shown to be associated with lower levels of disease-related markers of inflammation in adulthood^(26–30) and even earlier in life, in adolescence⁽³¹⁾. Non-nutritive polyphenolic

Abbreviations: age 11 IQ, intelligent quotient at age 11 years; Chol:HDL ratio, cholesterol:HDL-cholesterol ratio; CRP, C-reactive protein; IQ, intelligent quotient; LBC1936, Lothian Birth Cohort 1936.

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compounds such as flavonoids, present in plant-based foods and drinks, particularly fruit, vegetables, tea, red wine and cocoa, have significant antioxidant and anti-inflammatory activity⁽³²⁾, and have emerged in recent years as an important component in the relationship between diet and inflammation^(33–38) and with cardiovascular health⁽³⁹⁾. It is unclear whether specific food components such as antioxidants and flavonoids are responsible for the apparent protective role of nutrient-dense dietary patterns and foods.

Often, any change in risk associated with high levels of inflammatory biomarkers disappears after multivariate adjustment for behavioural factors. For example, high concentrations of CRP have been reliably associated with obesity^(40–42), the metabolic syndrome⁽⁴³⁾ and smoking^(44,45). In addition to behavioural correlates, there is also evidence to support a link between cognitive ability and inflammation. Not only is cognition associated with systemic inflammation in adulthood, but also poor cognitive ability earlier in life predicts increased inflammation in middle age^(46,47) and later life⁽⁴⁸⁾ and an increased risk of death from inflammatory-associated diseases⁽⁴⁹⁾. Often, full consideration is not given to the role of potential confounders, especially prior cognitive ability, as these data are rarely available.

The present study attempts to address three main gaps in the literature. First, studies that assess diet–inflammation associations using multiple dietary indicators in the same individuals are lacking. Without this, misleading conclusions can be drawn about the putatively protective role of a single dietary measure. Second, there are few studies conducted exclusively within old age groups. Ageing is associated with increases in several inflammatory markers, and there is strong evidence that these markers influence age-associated pathology⁽⁵⁰⁾. Third, we examined diet–inflammation associations in a well-characterised community-dwelling Scottish cohort, of mean age 70 years, for whom there were validated intelligent quotient (IQ) scores from youth, in order to control for prior cognitive ability. We examined two commonly used circulating markers of inflammation (plasma CRP and fibrinogen) that measure different aspects of the inflammatory process, in the same elderly sample, with a view to determining whether the inverse diet–inflammation relationships previously reported are a result of dietary patterns, single foods, or more specific aspects of nutrition.

Methods

Study population

The Lothian Birth Cohort 1936 (LBC1936) study includes 1091 men and women, all of whom were born in 1936 and who were living independently in the community at about 70 years of age. Almost all participants were resident in Edinburgh and the surrounding Lothian region at recruitment in older age. Early-life (mean age 11 years) intelligence test data were available for most of this sample, because most were surviving participants of the Scottish Mental Survey of 1947⁽⁵¹⁾. Assessment in later life took place between 2004 and 2007 when participants were aged about 70 years

(mean 69.5 (SD 0.8)). Full recruitment and testing procedures have been reported in an open-access protocol paper^(52,53). The assessment at age 70 years involved detailed cognitive, biomedical and psychosocial testing. FFQ data were available for 882 participants. We excluded ninety participants with a CRP measure >10 mg/l (to omit possible acute illness). After exclusion, 792 individuals remained for the present analyses. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from the Lothian Research Ethics Committee for Scotland (LREC/2003/2/29). Written informed consent was obtained from all subjects/patients.

Assessment of dietary intake

Dietary data were derived from the Scottish Collaborative Group 168-item FFQ, version 7.0^(54,55). This semi-quantitative FFQ was developed for use in older adults (see <http://www.foodfrequency.org.uk>)⁽⁵⁶⁾. A common unit or portion size for each food or drink item is specified, and responses are marked according to a nine-point scale, ranging from 'rarely or never' to '7+ per d' to describe the typical amount and frequency of each food consumed. All participants were asked to complete the FFQ at home and return it by post. Estimation of food and nutrient intake was carried out at the University of Aberdeen using an in-house programme and the latest available information in the UK food composition tables. The repeatability and validity of the FFQ was demonstrated against 4 d weighed food diaries; dietary intake in later life was found to be reasonably stable in the short term, and the authors reported good validity for most nutrients in community-dwelling older populations^(54,57). Intake of antioxidant nutrients and flavonoids, and dietary pattern scores were adjusted for overall energy intake using the residual method⁽⁵⁸⁾.

Dietary patterns. Dietary patterns were extracted via principal components analysis with orthogonal rotation from all FFQ items. Further description of their ascertainment can be found in Möttus *et al.*⁽⁵⁹⁾. The Mediterranean dietary pattern was primarily defined by greater consumption of vegetables (such as leeks or courgettes, broccoli, and salad vegetables), fish, poultry, pasta, rice, water, tomato-based sauces, oil and vinegar dressing, and beans. The 'health-aware' dietary pattern was mainly characterised by a high intake of fruits (e.g. apples, bananas, tinned fruits, oranges and others) and carrots, and low consumption of meat products (bacon or gammon, pork or lamb, and sausages), eggs, and spirits or liqueurs. Participants obtained a score for each dietary pattern, indicating the degree to which the individual's diet conformed to that pattern, where the mean score is 0.

Fruit and vegetables. Total (fresh) fruit and vegetable intakes were calculated independently and in combination. Fruit included fresh fruit salad, apples, bananas, oranges, satsumas, grapefruit, pears, peaches, nectarines, kiwi fruit, grapes, strawberries, melons and other fresh fruits. Vegetables included peas, green beans, carrots, cabbage, Brussels



sprouts, spinach, spring greens, leeks, courgettes, cauliflower, swede, turnips, sweetcorn, onions, tomatoes, sweet peppers, and other salad vegetables such as lettuce, cucumber, etc.

Flavonoid-rich foods. Intakes of flavonoid-rich foods (chocolate, apples and citrus fruits) and drinks (tea and red wine) were analysed.

Flavonoid subclasses. Intakes of a selection of five flavonoid subclasses (flavonols, flavones, catechins, proanthocyanidin type B and flavanones) were estimated using a UK flavonoid database, which included 396 items⁽⁶⁰⁾.

Antioxidant nutrients. Dietary intake of antioxidant nutrients (vitamin C, vitamin E, β -carotene, Zn and Se) was estimated using the FFQ data.

Assessment of inflammatory markers

Serum CRP (mg/l) and fibrinogen (g/l) were extracted from blood samples that were collected intravenously by nurses as part of the participants' clinical assessment. The CRP assay was performed using a dry-slide immuno-rate method on OrthoFusion 5.1 F.S analysers (Ortho Clinical Diagnostics). The CRP assay method has low sensitivity in the lower range of CRP values; approximately 58% of the participants fell into a single lowest category (1.5 mg/l). Therefore, in the analyses, and as in Möttus *et al.*⁽⁵⁹⁾, all CRP values were collapsed into two categories: ≤ 3 mg/l (normal; including the measured values of 1.5 and 3 mg/l) and > 3 mg/l (elevated; including the rest of the values). Besides being meaningful for the current distribution of CRP values, the relevance of the 3 mg/l cut-off has been suggested for the prediction of CVD⁽⁶¹⁾. The fibrinogen assay was performed using an automated Clauss assay (TOPS coagulometer; Instrumentation Laboratory). The range of fibrinogen values was 1.5–6.0 g/l.

Assessment of covariates

General demographic information, including sex (1 = male, 2 = female), age (exact age in days at the time of assessment) and years of full-time education, was assessed and coded accordingly. Childhood cognitive ability was derived from scores on the Moray House Test taken at age 11 years⁽⁵²⁾. The Moray House Test is a group-administered test of general intelligence. This test was concurrently validated against the Terman–Merrill revision of the Binet scales⁽⁶²⁾. The scores were converted to standard IQ-type scores for the whole sample (n 1091), with a mean value of 100 and a standard deviation of 15. Adult occupational social class was derived from each participant's highest reported occupation and classified into one of six categories ranging from I (professional occupations) to V (unskilled occupations), with III divided into IIIN (non-manual) and IIIM (manual)⁽⁶³⁾. For data analysis, occupational social classes IV and V were combined due to the small number of participants in each class. Height and weight were measured by trained research nurses as part of a physical examination. BMI was calculated as weight (kg) divided by height squared (m^2). Smoking status was coded as 0 (never smoker), 1 (ex-smoker) or 2 (current smoker). Physical activity was the number of days

of sport or physical exercise (e.g. dancing or brisk walking) per average month. A self-reported history of CVD, hypertension, stroke and diabetes was recorded by a trained interviewer at the time of assessment and coded as dichotomous variables (0 = no, 1 = yes). The cholesterol:HDL-cholesterol ratio (Chol:HDL ratio) was obtained from a blood sample drawn on the day of assessment. The Chol:HDL ratio provides a strong prediction of CHD risk; a lower ratio is clinically more desirable.

Statistical analyses

All statistical analyses were performed using SPSS version 19 (IBM). The associations between potential covariates and inflammatory biomarkers were tested using regression analyses. For CRP (elevated *v.* normal), we performed logistic regression analyses, and for fibrinogen (continuous), we performed linear regression analyses. In the main analyses, we used three models to examine the associations between dietary predictor variables and inflammatory biomarkers. All categorical variables were treatment coded. Model 1 included sex and exact age in days at the time of assessment. In model 2, IQ at age 11 years (age 11 IQ) was added to adjust for any confounding effects of childhood cognitive ability; childhood IQ was previously found to be an independent predictor of CRP in this sample⁽⁴⁸⁾. In model 3, to control for potentially confounding lifestyle factors and health variables, we added occupational social class, BMI, physical activity, smoking status, history of CVD, hypertension, Chol:HDL ratio, stroke and diabetes to model 2. The effects are reported using unstandardised β regression coefficients for CRP analyses, and standardised β regression coefficients for fibrinogen analyses. *P* values are reported. The 0.05 level of significance was used for all data analyses.

Results

The characteristics of the study participants are presented in Table 1. A total of 792 participants (48% men) with a mean age of 69.5 years (*SD* 0.85) were included in the analyses. Nearly half (48%) were never smokers and 9% were current smokers, the mean BMI was 27.4, and 23.6% reported a history of CVD, 38.3% of hypertension, 3.5% of stroke and 7.2% of diabetes. Of the participants, 42% had an elevated CRP level of ≥ 4 mg/l. Pearson's correlation coefficient (*r*) between inflammatory biomarkers, CRP and fibrinogen was 0.287 ($P < 0.001$). Table 2 presents the unadjusted associations (derived from logistic/linear regression analyses) between CRP, fibrinogen and covariates. A higher level of CRP was associated with being older (even in this narrow-age cohort), a lower age 11 IQ, a history of smoking, a higher BMI (all $P < 0.01$), a less-professional social class ($P = 0.028$), a diagnosis of hypertension ($P < 0.001$) and diabetes ($P = 0.02$), and a higher (less-desirable) Chol:HDL ratio ($P = 0.004$), but not with CVD or stroke. A higher level of fibrinogen was associated with being younger ($P = 0.002$), a lower age 11 IQ ($P = 0.018$), a history of smoking ($P = 0.005$), a higher BMI ($P = 0.047$), and a history of hypertension ($P = 0.002$),



Table 1. Characteristics of the study population from the Lothian Birth Cohort 1936 (LBC1936; *n* 792)

(Number of participants; mean values and standard deviations; number of participants and percentages)

Characteristics	<i>n</i>	Mean	SD
Demographic and lifestyle			
Age (years)	792	69.5	0.85
Male	792		
<i>n</i>	383		
%	48.4		
Age 11 IQ	748	101.6	14.0
Education (full time, years)	792	10.8	1.1
Occupational class	776		
I			
<i>n</i>	147		
%	18.9		
II			
<i>n</i>	303		
%	39.0		
IIIN			
<i>n</i>	187		
%	24.1		
IIIM			
<i>n</i>	116		
%	14.9		
IV and V*			
<i>n</i>	23		
%	3.0		
Smoking status	792		
Never smoker			
<i>n</i>	383		
%	48.4		
Ex-smoker			
<i>n</i>	337		
%	42.6		
Current smoker			
<i>n</i>	72		
%	9.1		
BMI	791	27.4	4.1
Physical activity (d/month)	779	7.88	8.1
CVD diagnosis	792		
<i>n</i>	187		
%	23.6		
Hypertension diagnosis	792		
<i>n</i>	303		
%	38.3		
Chol:HDL ratio	685		
<3.5			
<i>n</i>	287		
%	41.9		
3.5– <5			
<i>n</i>	325		
%	47.4		
≥5			
<i>n</i>	73		
%	10.7		
Stroke diagnosis	792		
<i>n</i>	28		
%	3.5		
Diabetes diagnosis	792		
<i>n</i>	57		
%	7.2		
Plasma markers of inflammation			
CRP†	766		
Normal (≤3 mg/l)			
<i>n</i>	448		
%	58.5		
Elevated (>3 mg/l)			
<i>n</i>	318		
%	41.5		
Fibrinogen (g/l)	770	3.2	0.58

Table 1. Continued

Characteristics	<i>n</i>	Mean	SD
Dietary intake			
Dietary patterns (factor scores)‡			
Mediterranean dietary pattern	792	0.01	0.99
Health-aware dietary pattern	792	0.03	1.0
Fruit and vegetables (measures per d)			
Total fruit	792	2.5	2.4
Total vegetables	792	3.1	2.4
Total fruit and vegetables	792	5.6	4.0
Flavonoid-rich foods (measures per d)			
Tea	790	2.5	2.0
Red wine	791	0.33	0.76
Chocolate	790	0.55	0.70
Apples	792	0.44	0.59
Citrus fruits	792	0.41	0.58
Dietary flavonoids‡			
Flavonols	792	37.6	24.5
Flavones	792	0.29	0.20
Catechins	792	185.5	137.9
Proanthocyanidins	792	52.6	34.3
Flavonones	792	25.6	25.7
Dietary intakes (per d)‡			
Vitamin C (mg)	792	107.3	60.3
Vitamin E (μg)	792	8.0	3.6
β-Carotene (μg)	791	2778.0	2112.3
Zn (mg)	792	8.8	2.8
Se (μg)	792	48.2	19.2

Age 11 IQ, intelligent quotient at age 11 years; IIIN, non-manual; IIIM, manual; Chol:HDL ratio, cholesterol:HDL-cholesterol ratio; CRP, C-reactive protein.

* Occupational social classes IV and V were combined due to the small number of participants in each class.

† Participants with a CRP measure >10 mg/l were excluded (*n* 90) to omit possible acute illness.

‡ Adjusted for total energy intake.

stroke ($P=0.002$) and diabetes ($P=0.001$), but not with CVD or Chol:HDL ratio. Table 3 presents the unadjusted associations (derived from linear regression analyses) between the dietary patterns and covariates. A higher Mediterranean pattern score was associated with being younger ($P=0.015$), a higher age 11 IQ ($P=0.002$), less smoking ($P<0.001$), being female ($P=0.002$) and a lower Chol:HDL ratio ($P=0.028$). A higher health-aware dietary pattern score was associated with less smoking ($P<0.001$), a lower BMI ($P=0.015$), more physical activity ($P=0.037$) and being female ($P<0.001$).

Table 4 shows the results of the main regression analyses for all dietary measures (variously adjusted in three models).

Diet and C-reactive protein

First, we performed logistic regression analyses on the associations between diet and CRP (normal *v.* elevated levels). In the basic age- (in d) and sex-adjusted models (model 1), a lower CRP level (≤ 3 mg/l) was associated with a higher health-aware dietary pattern score, a higher intake of fresh fruit including flavonoid-rich apples and citrus fruits, and combined fruit and vegetables, dietary vitamin C, and flavanones (found in citrus fruits). Additionally adjusting for the potential confounding effects of higher childhood cognitive ability (model 2) made little difference to effect sizes. Further adjustment for occupational social class, BMI, physical activity, smoking status, Chol:HDL ratio, and history of CVD, stroke



Table 2. Univariate associations between C-reactive protein (CRP) and fibrinogen levels and covariates (Unstandardised and standardised β regression coefficients; mean values and standard deviations)

Characteristics	CRP (mg/l)*				Fibrinogen (g/l)†			
	Unstandardised β	Mean	SD	P	Standardised β	Mean	SD	P
Age	0.215			<0.001	-0.112			0.002
Age 11 IQ	-0.128			0.001	-0.088			0.018
BMI	0.262			<0.001	0.072			0.047
Physical activity‡	-0.026			0.339	-0.049			0.180
Sex	0.009			0.795	0.057			0.115
Male		3.38	2.4			3.17	0.59	
Female		3.45	2.5			3.24	0.56	
Occupational class	0.080			0.028	0.044			0.223
I		3.12	2.2			3.15	0.57	
II		3.38	2.5			3.20	0.58	
IIIN		3.38	2.4			3.24	0.56	
IIIM		4.04	2.5			3.18	0.63	
IV and V§		3.41	2.4			3.36	0.48	
Smoking status	0.088			0.015	0.103			0.004
Never smoker		3.17	2.2			3.18	0.56	
Ex-smoker		3.51	2.5			3.18	0.57	
Current smoker		4.32	2.9			3.48	0.60	
CVD	0.026			0.473	0.050			0.165
No		3.40	2.4			3.19	0.56	
Yes		3.48	2.4			3.26	0.63	
Hypertension	0.129			<0.001	0.112			0.002
No		3.21	2.4			3.15	0.54	
Yes		3.77	2.4			3.29	0.62	
Chol:HDL ratio	0.109			0.004	0.045			0.244
<3.5		3.27	2.4			3.16	0.57	
3.5–<5.0		3.46	2.4			3.23	0.59	
≥5.0		4.32	2.7			3.20	0.57	
Stroke	0.003			0.934	0.112			0.002
No		3.40	2.4			3.19	0.56	
Yes		3.96	3.1			3.54	0.81	
Diabetes	0.084			0.020	0.117			0.001
No		3.35	2.4			3.19	0.57	
Yes		4.33	2.7			3.45	0.63	

Age 11 IQ, intelligent quotient at age 11 years; IIIN, non-manual; IIIM, manual; Chol:HDL ratio, cholesterol:HDL-cholesterol ratio.
 *Unstandardised β regression coefficients and P values were derived from logistic regression analyses (CRP: normal (≤ 3 mg/l) v. elevated (> 3 mg/l)).
 †Standardised β regression coefficients and P values were derived from linear regression analyses.
 ‡Physical activity was the number of days of sport or physical exercise per month.
 §Occupational social classes IV and V were combined due to the small number of participants in each class.

and diabetes (model 3) caused some of these associations to lose significance. In the final model, the dietary measures associated with a lower CRP concentration (at $P < 0.05$) were the 'health-aware' (low-fat) dietary pattern (unstandardised $\beta = (0.200, \text{OR } 0.82, 95\% \text{ CI } 0.68, 0.99)$ and fruit intake (unstandardised $\beta = (0.100, \text{OR } 0.91, 95\% \text{ CI } 0.82, 0.99)$, including flavonoid-rich apples (unstandardised $\beta = (0.456, \text{OR } 0.63, 95\% \text{ CI } 0.439, 0.946)$). No significant association was found with vegetable intake (independently) and CRP.

Diet and fibrinogen

Second, we performed linear regression analyses on the associations between diet and fibrinogen. In the basic age- (in d) and sex-adjusted models (model 1), a lower fibrinogen level was associated with a higher Mediterranean dietary pattern score and a higher intake of fruit and vegetables, flavonoid-rich red wine and chocolate, and diet-derived vitamin C. With the exception of a higher intake of vegetables and chocolate, these inverse associations remained significant

after controlling for childhood cognitive ability (in model 2). Further adjustment for lifestyle and health covariates (in model 3) caused some associations to lose significance. Robust inverse associations (all at $P < 0.05$) were observed between fibrinogen and the Mediterranean dietary pattern (standardised $\beta = (0.100)$, fruit intake (standardised $\beta = (0.083)$, and combined fruit and vegetable intake (standardised $\beta = (0.084)$.

Discussion

In the present large sample of community-dwelling older adults aged approximately 70 years, healthy dietary patterns rich in fresh produce, especially fruit, were associated with lower concentrations of two common biomarkers of systemic low-grade inflammation. Closer adherence to a Mediterranean diet was related to lower fibrinogen, but not CRP concentrations. Instead, a lower CRP level was associated with a 'prudent' (health-aware) dietary pattern comprising fruit and low-fat foods. It is noteworthy that these relationships

Table 3. Univariate associations between the Mediterranean and health-aware dietary pattern factor scores and covariates (Unstandardised and standardised β regression coefficients; mean values and standard deviations)

Characteristics	Mediterranean				Health-aware			
	Unstandardised β	Mean	SD	P	Standardised β	Mean	SD	P
Age	−0.087			0.015	0.038			0.291
Age 11 IQ	0.112			0.002	−0.039			0.290
BMI	−0.032			0.370	−0.087			0.015
Physical activity*	0.053			0.142	0.075			0.037
Sex	0.112			0.002	0.331			<0.001
Male		−0.10	0.86			−0.31	1.0	
Female		0.12	1.1			0.35	0.91	
Occupational class	−0.272			<0.001	−0.002			0.945
I		0.44	1.1			−0.07	1.1	
II		0.12	1.1			0.08	0.95	
IIIN		−0.17	0.78			0.20	0.90	
IIIM		−0.42	0.71			−0.23	0.97	
IV and V†		−0.25	0.96			−0.04	1.6	
Smoking status	−0.070			0.048	−0.191			<0.001
Never smoker		0.03	0.91			0.19	0.94	
Ex-smoker		0.06	1.1			−0.03	1.0	
Current smoker		−0.35	0.89			−0.52	1.1	
CVD	−0.030			0.392	−0.026			0.466
No		0.03	1.0			0.05	0.99	
Yes		−0.04	0.85			−0.02	1.0	
Hypertension	−0.038			0.283	0.026			0.461
No		0.042	1.1			0.01	0.97	
Yes		−0.036	0.85			0.064	1.1	
Chol:HDL ratio	−0.084			0.028	0.000			0.996
<3.5		0.99	1.1			0.03	1.0	
3.5–<5.0		−0.033	0.90			0.04	0.98	
≥5.0		−0.15	0.80			0.02	1.2	
Stroke	−0.028			0.438	0.015			0.681
No		0.01	0.99			0.03	1.0	
Yes		−0.13	0.86			0.11	1.1	
Diabetes	−0.053			0.134	0.035			0.320
No		0.02	0.98			0.02	1.0	
Yes		−0.18	0.99			0.16	0.95	

Age 11 IQ, intelligent quotient at age 11 years; IIIN, non-manual; IIIM, manual; Chol:HDL ratio, cholesterol:HDL-cholesterol ratio.

* Physical activity was the number of days of sport or physical exercise per month.

† Occupational social classes IV and V were combined due to the small number of participants in each class.

remained significant after adjusting for variables that reflected a healthy lifestyle, such as smoking, BMI and physical activity, factors strongly associated with a high concentration of inflammatory biomarkers^(41,44), and for a history of major chronic diseases. Interestingly, consumption of vegetables *per se* and specific food components (antioxidant nutrients and various subclasses of flavonoids) failed to show statistically significant relationships with either of the biomarkers. A key finding from the present study, and contrary to expectations, was that the significant relationship between diet and inflammation remained after adjusting for childhood cognitive ability, previously shown to be an important predictor of both diet choices^(64,65), including flavonoid consumption⁽⁶⁶⁾, and inflammation^(46–48) in adulthood, and inversely associated with both CRP and fibrinogen in this sample. The data suggest that habitual dietary patterns may independently relate to inflammation in later life.

A large literature links healthy dietary patterns, especially the Mediterranean diet, with positive health outcomes⁽⁶⁷⁾, including lower levels of systemic inflammation. A recent systematic review by Barbaresko *et al.*⁽⁴⁾ has concluded that fruit and vegetable-based 'healthy' dietary patterns are

associated with lower biomarkers of inflammation including CRP, and that this finding is particularly well-supported by intervention studies with the Mediterranean diet^(68–70). In a 2-year intervention study, subjects who were administered a Mediterranean diet (rich in vegetables, fruit, nuts, olive oil and whole grains) experienced a significant decline in CRP levels, which was not found in the control group⁽⁶⁸⁾. This applied to all biomarkers of inflammation measured, particularly CRP. Closer adherence to a Mediterranean-type diet in observational studies has been shown to be associated with lower levels of CRP and fibrinogen^(6,7,21,24,71), thus providing more evidence that this dietary pattern and its constituents may help to lower low-grade inflammation. One further study found that CRP levels, although not significantly associated with the Spanish Mediterranean diet, were lowest in subjects with the highest consumption of olive oil and nuts, the major components of this pattern⁽⁷²⁾. However, some trials in Northern European populations, such as Germany, have found no effect of the Mediterranean diet on the levels of CRP or fibrinogen⁽⁷³⁾. It is possible that the observed associations between 'prudent' dietary patterns and inflammatory markers may be indirect. Healthy foods and snacks may



Table 4. Multivariate associations between C-reactive protein (CRP) and fibrinogen levels and dietary factors at age 70 years (Unstandardised and standardised β regression coefficients)

Predictors	CRP (mg/l)*			Fibrinogen (g/l)†		
	Model 1‡	Model 2§	Model 3	Model 1‡	Model 2§	Model 3
	Unstandardised β	Unstandardised β	Unstandardised β	Standardised β	Standardised β	Standardised β
Dietary patterns						
Mediterranean	-0.141	-0.120	-0.078	-0.133***	-0.123**	-0.100*
Health-aware	-0.291**	-0.293**	-0.200*	0.023	0.014	0.009
Fruit and vegetables						
Total fruit	-0.109**	-0.117**	-0.100*	-0.088*	-0.089*	-0.083*
Total vegetables	-0.065	-0.060	-0.033	-0.072*	-0.071	-0.057
Total FV	-0.062**	-0.062**	-0.044	-0.097**	-0.096*	-0.084*
Flavonoid-rich foods						
Tea	0.015	-0.005	-0.010	-0.007	-0.015	-0.014
Red wine	-0.010	-0.032	0.048	-0.133***	-0.101**	-0.073
Chocolate	-0.067	-0.016	-0.048	-0.078*	-0.068	-0.059
Apples	-0.441**	-0.522**	-0.456*	-0.007	-0.036	-0.037
Citrus fruits	-0.369*	-0.395*	-0.337	-0.055	-0.032	-0.018
Flavonoids						
Flavonols	0.000	-0.002	-0.002	-0.003	-0.015	0.010
Flavones	0.194	0.088	-0.190	-0.025	-0.048	-0.065
Catechins	0.000	0.000	0.000	0.000	-0.007	0.019
Proanthocyanidins	0.000	-0.002	-0.002	-0.029	-0.032	-0.004
Flavanones	-0.008*	-0.010*	-0.007	-0.049	-0.028	-0.013
Antioxidant nutrients						
Vitamin C	-0.003*	-0.003*	-0.002	-0.099**	-0.093*	-0.074
Vitamin E	0.005	0.007	0.028	-0.010	-0.005	0.007
β -Carotene	0.000	0.000	0.000	-0.042	-0.048	-0.054
Zn	0.000	0.000	-0.017	-0.055	-0.056	-0.054
Se	-0.004	-0.004	-0.005	-0.051	-0.051	-0.055

FV, fruit and vegetables; age 11 IQ, intelligent quotient at age 11 years.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

* Unstandardised β regression coefficients and P values were derived from logistic regression analyses (CRP: normal (≤ 3 mg/l) v. elevated (> 3 mg/l)).

† Standardised β regression coefficients and P values were derived from linear regression analyses.

‡ Model 1 was adjusted for age and sex.

§ Model 2 was adjusted for age, sex and age 11 IQ.

|| Model 3 was adjusted for age, sex, age 11 IQ, occupational social class, BMI, physical activity, cholesterol:HDL-cholesterol ratio, smoking status, and history of CVD, hypertension, stroke and diabetes.

be consumed at the expense of unhealthy, sugary or fatty (pro-inflammatory) foods. Following intake of energy-dense, nutrient-poor, processed foods, meal-induced inflammation has been evidenced by immediate increases in inflammatory biomarkers such as CRP⁽⁷⁴⁾. In population studies, Western-type dietary pattern components such as red meat, high-fat dairy and other sources of saturated fat, and refined carbohydrates show positive associations with biomarkers such as CRP and fibrinogen^(2,18,20,22,75,76).

Studying dietary patterns has a number of advantages over the 'single food or nutrient' approach. Foods and nutrients are rarely eaten in isolation, whereas dietary patterns capture the complexity of diets and synergistic interactions among nutrients in addition to different food sources of the same nutrient⁽⁷⁷⁾. However, a large number of epidemiological and intervention studies have focused specifically on fruit and vegetable intake as single food components. Fruit and vegetables are a rich source of beneficial compounds including vitamins, carotenoids, polyphenols and other bioactive compounds, which make them a food group with a high dietary antioxidant capacity and multiple anti-inflammatory actions^(78,79). No association was found between CRP and fruit and vegetables intake in a sample at high risk for CVD⁽⁷²⁾; however, many other observational studies have

reported potentially beneficial effects of fruit and vegetable intake on CRP in adulthood^(15–17,80) even after adjusting for BMI, smoking and other covariates. CRP has been shown to decrease as fruit and vegetables consumption increases. One intervention study placed healthy non-smoking men on diets containing only two servings per d of fruits and vegetables for 4 weeks and then placed them on diets of increasing fruit and vegetable consumption for another 4 weeks. Those who were randomised to eight fruit/vegetable servings (but not five servings) per d had a significant decline in CRP levels⁽⁸¹⁾. The lack of association of vegetable intake with the biomarkers of inflammation in our sample may be due to cultural differences; in Scotland, vegetable consumption is lower than in the UK average⁽⁸²⁾ and markedly lower than in Mediterranean populations where, on average, greater importance is placed on fresh produce⁽⁸³⁾. Our data support the findings of two other UK studies: the British Regional Heart Study, which reported inverse associations with CRP and fruit intake but not with vegetable intake in older men⁽²⁵⁾, and a longitudinal (6-year) investigation finding no independent association with overall vegetable intake⁽¹⁰⁾. Deep-rooted cultural differences in diet can make comparisons between studies problematic. Furthermore, many studies reporting significant associations with biomarkers have

assessed fruit and vegetable intake in combination only^(14,80,84); therefore, it is unclear whether a particular dietary component is driving the associations.

Anti-inflammatory benefits with increased fruit and vegetable intake have often been attributed to the effect of specific antioxidant nutrients, such as β -carotene, Zn and vitamin C, since oxidative stress is an underlying mechanism for several chronic diseases^(85,86). Brighenti *et al.*⁽⁷⁸⁾ reported that CRP levels were progressively lower with increasing levels of antioxidant capacity of the diet, estimated from dietary intake of fruits, vegetables and other foods. However, a Catalan study has failed to find any association between CRP and β -carotene, vitamin C or vitamin E⁽⁸⁷⁾. Among the five antioxidant nutrients assessed in the present analysis, only one (vitamin C) was found to have a potentially beneficial effect on inflammation (fibrinogen). This finding was probably due to the vitamin C content in fruit; however, this association narrowly missed significance following multivariate adjustment. In another study, reduced CRP and fibrinogen concentrations were associated with a higher intake of dietary vitamin C, but not with other antioxidant nutrients tested⁽⁸⁸⁾. A decrease in inflammation status associated with a higher intake of dietary vitamin C is supported by other population studies in middle-aged and elderly people^(16,25) and in some clinical trials⁽²⁹⁾. In general, the results of the present study suggest that, with the possible exception of food-derived vitamin C, intake of antioxidant nutrients does not explain the inverse diet–inflammation associations. Furthermore, epidemiological studies have consistently shown that increased fruit and vegetable intakes are associated with a lower risk of cardiovascular events^(89,90). Yet, supplementation with several of these antioxidant nutrients in clinical trials and intervention studies has not demonstrated a concomitant decline in the risk of CVD^(91,92).

Previous studies have found that intake of dietary flavonoids is inversely associated with inflammatory diseases⁽³²⁾ and serum CRP concentrations^(34,42). Of the flavonoid-rich foods and drinks assessed in this sample, only apples were associated with lower inflammation (CRP). Consistent with the results of the present investigation, Chun *et al.*⁽³⁴⁾ observed that consumption of apples, a rich source of flavonoids, was associated with lower CRP concentrations. Several clinical trials have supported the link between flavonoid consumption and reduced CRP concentrations⁽⁹³⁾, but not all⁽⁹⁴⁾. We observed no relationship between several flavonoid subclasses, contrary to other studies. For example, several flavonoid subclasses (flavones, flavanones and total flavonoids) were associated with lower concentrations of some inflammatory biomarkers in the Nurses' Health Study⁽³⁸⁾. However, data on the associations between flavonoids and inflammation are still considered controversial, and inaccurate estimates of flavonoid intake from the diet are based on often incomplete flavonoid food composition data and, therefore, inconsistent findings may arise⁽³⁴⁾.

The present study was limited by the cross-sectional nature of the data; therefore, the observed associations might not be causal. Given the older age of participants, reverse causation is possible. Certain low-grade inflammatory states such as mild

malaise could have an easy impact on diet, and some individuals with a history of chronic disease (related to inflammation, perhaps) might have altered their diets according to health recommendations before assessment. Other limitations in using this dataset include the use of a self-report measure of dietary consumption; self-reports may be biased. However, the validity of the FFQ has previously been reported in an old-age sample^(54,55). As a self-selected volunteer sample of a narrow older age and specific geographical location with high cultural homogeneity, the findings from the LBC1936 cohort may not generalise to other populations.

A strength of the present study was the use of a well-characterised sample population, with available measures of diet, biomarkers of interest, and comprehensive health and lifestyle information. We used an age-homogeneous population, minimising age and cohort effects. This is important as CRP and fibrinogen increase with age, and the effect of potential confounding factors can vary according to lifelong exposure⁽⁵⁾. Some chronic low-grade inflammation patterns found in the elderly may be related to co-morbidities; however, it is also observed in 'successful ageing'⁽⁵⁰⁾. The heterogeneity among reported associations with diet in studies may be due to the use of different inflammatory markers and to the different physiological mechanisms involving each biomarker⁽⁴⁾. At present, there is no consensus as to which markers of inflammation best represent low-grade inflammation⁽⁵⁾. The present data expand previous knowledge obtained from observational studies, and lend further support to the evidence suggesting that diet may play a role in mediating the body's biological response to inflammation. However, further longitudinal and intervention studies are needed in order to determine a causal link. Because fruit and vegetable intake is consistently associated with a decreased risk of chronic diseases, public health strategies to improve fruit and vegetable intake should be encouraged. Dietary changes remain a low-risk intervention strategy.

In conclusion, our findings suggest that a Mediterranean dietary pattern and a 'prudent' (health-aware) dietary pattern, rich in fresh produce, are associated with lower plasma concentrations of CRP and fibrinogen in older age. The data are not supportive of a beneficial, independent effect of antioxidant nutrients or flavonoids. Dietary patterns represent a broader picture of food and nutrient consumption, and thus may be more predictive of disease risk than individual foods or nutrients.

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None of the authors has any conflict of interest to declare.

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Appendix C - LBC1936 Study Ethics Approval for Wave 1 (2004-2007)

Lothian NHS Board

Lothian Research Ethics Committee
Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
Fax 0131 536 9346
www.nhslothian.scot.nhs.uk



Dr J M Starr
Consultant General & Geriatric Medicine
Royal Victoria Hospital
Craigleith Road
Edinburgh

Date 18 April 2003
Your Ref
Our Ref **LREC/2003/2/29**

Enquiries to Dale Keir
Extension 89025
Direct Line 0131 536 9025
Email dale.keir@lhb.scot.nhs.uk

Dear Dr Starr,

MREC/01/0/56 - EARLY LIFE PREDICTORS OF COGNITIVE CHANGE AND PHYSICAL AND MENTAL HEALTH INEQUALITIES IN 1947 SCOTTISH MENTAL SURVEY COHORT

Thank you for submitting the above research proposal for local review of the "locality" issues. The Lothian Research Ethics Committee has agreed to give it a favourable local opinion, **subject to** management approval **also** being granted. An official Certificate of Local Opinion outlining the conditions of this opinion is enclosed: it is valid only in conjunction with written management approval from the Lothian NHS body/Trust(s) concerned. Please note that the LREC reference number LREC/2003/2/29 **must** be quoted on all correspondence. Correspondence received without the LREC reference number will be returned.

Under the terms of the Scottish Executive Health Department Research Governance Framework for Health and Community Care this opinion has been notified to the Research & Development Office of the relevant NHS Trust(s) where the research is intended to take place. It is the NHS Trust(s) from whom you must obtain management approval before any work on the proposed research can proceed.

The Lothian Research Ethics Committee is fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guideline for the conduct of trials involving the participation of human subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board (IEC/IRB).

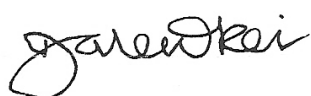


Headquarters
Deaconess House 148 Pleasance Edinburgh EH8 9RS

Chair Brian Cavanagh
Chief Executive James Barbour O.B.E.
Lothian NHS Board is the common name of Lothian Health Board

Details of the Lothian Research Ethics Committee and its documentation can be found on
http://www.nhslothian.scot.nhs.uk/nhs_lothian/about_lothian_health/lrec/index.html

Yours sincerely

A handwritten signature in black ink, appearing to read 'Dale Keir', with a stylized, cursive script.

DALE KEIR
Committee Administrator

cc *Dr Marlie MacLean*
Medical Research Council
20 Park Crescent
London
W1N 4AL

LOTHIAN RESEARCH ETHICS COMMITTEE

CERTIFICATE OF LOCAL REVIEW

LREC Reference Number: LREC/2003/2/29

Title: MREC/01/0/56 - Early life predictors of cognitive change and physical and mental health inequalities in 1947 Scottish Mental Survey cohort

Researcher: Dr J M Starr

The Lothian Research Ethics Sub-Committee has agreed that this proposed study is appropriate to be carried out in the Lothian Area subject to relevant management approval. This opinion encompasses all "locality issues" aspects of the application including the Patient/Subject Information Sheet and all other accompanying documentation provided as detailed in the Response Form issued by the MREC.

The MREC Annexe D, protocol, subject information sheet, information on compensation arrangements, payments to researchers and the provision of expenses to subjects were reviewed and approved (where appropriate).

The membership of the Lothian Research Ethics Committee is shown below:

Dr A K Zealley (Consultant)(M)(Chair)
Mr A B Dunlop (Lay)(M)
Dr D Marshall (GP)(M)
Dr M Logan (Consultant)(M)
Dr M S Macmillan (Lay)(F)
Professor P Hayes (Consultant)(M)
Mrs R Caborn (Lay)(F)
Mr N A Elliott-Cannon (Lay)(M)

Professor D J Webb (Consultant)(M)
Dr A Richardson (Consultant)(F)
Dr C P West (Consultant)(F)
Dr J Ironside (Consultant)(F)
Mr S Sikora (Nurse)(M)
Dr N Bateman (Consultant)(M)
Mrs D M Anderson (Lay)(F)
Dr R Hardie (Consultant)(F)

It is a condition of this opinion that you **must** obtain appropriate management approval from the relevant NHS body under the auspices of which the research is intended to take place **before** starting the study. It is that NHS body which has the responsibility of deciding whether or not the research should go ahead taking account of the opinion of the Multi-Centre Research Ethics Committee and Local Research Ethics Committee. It is also a condition that you are required to notify the Lothian Research Ethics Committee and the relevant NHS body, in advance, of any significant proposed deviation from the original protocol or application form. Reports to the relevant NHS body are also required once the research is underway if there are any unusual or unexpected results which raise questions about the safety of the research.

Researchers are also required to report on success, or difficulties, in recruiting subjects in order to provide useful feedback on perceptions of the project among patients and volunteers.



Peter Reith
Secretary
Lothian Research Ethics Committee



Dale Keir
Administrator
Lothian Research Ethics Committee

18 April 2003

**Appendix D - LBC1936 Recruitment Flowchart for Wave 1
(2004-2007)**

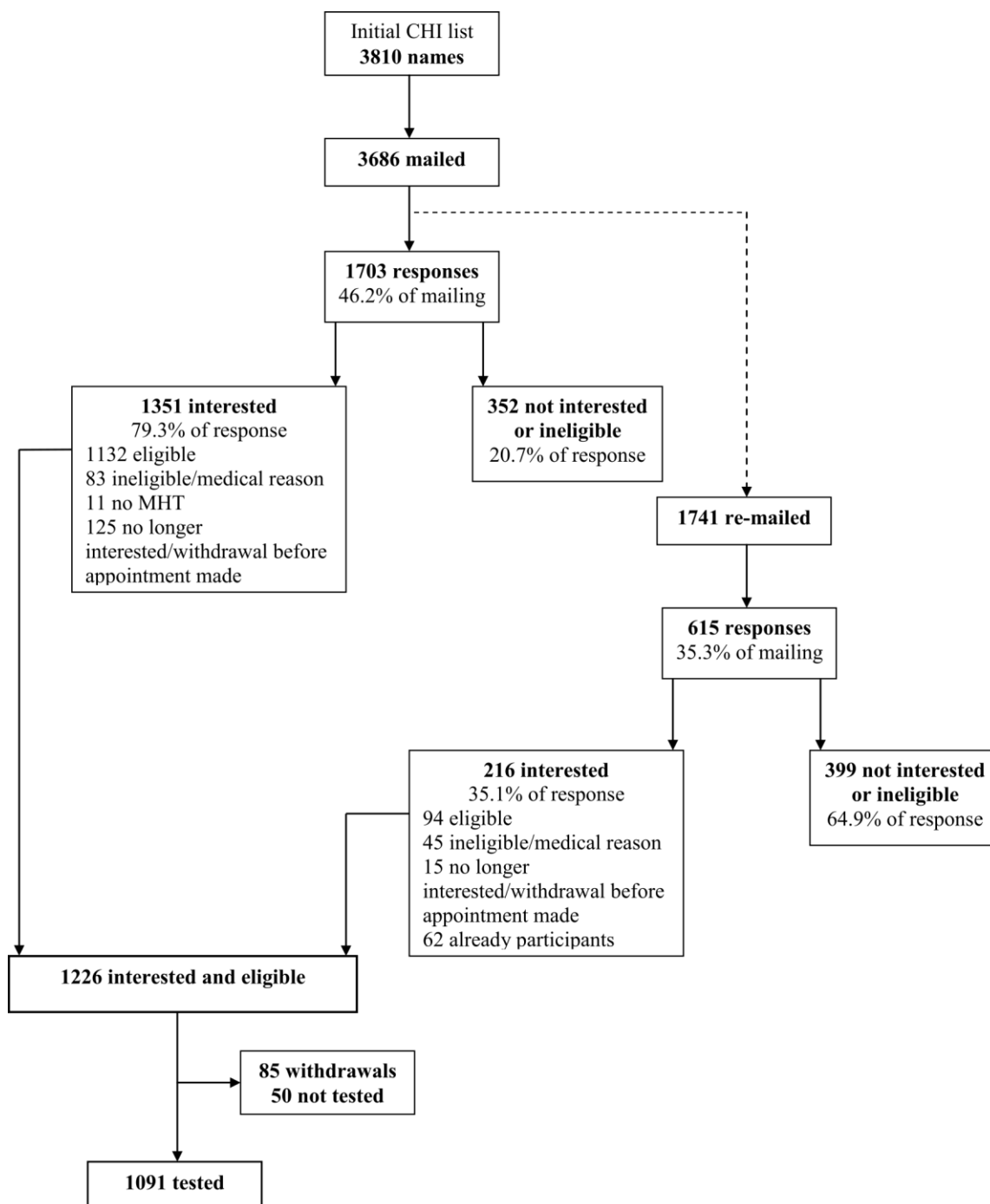


Figure 2. LBC1936 study recruitment flowchart

Appendix E - LBC1936 Participant Information for Wave 1
(2004-2007)

LBC1936 welcome letter at wave 1

PARTICIPANT DETAILS

DATE

LOTHIAN BIRTH COHORT 1936 STUDY

I'd like to invite you to take part in the Lothian Birth Cohort 1936 (LBC1936) study. The study is about the health of all people living in Scotland who were born in 1936. As I shall explain, it is unique and could not be conducted anywhere else in the world. You are part of a very special group, and I hope you will agree to become a member of the study.

We are trying to find out about the health and well-being of people as they grow older. Most studies of this type lack information about people from when they were younger. Scotland is unique. In 1947 it conducted the Scottish Mental Survey in which everyone born in 1936 took part. This means that Scotland is alone in the world in having information on the reasoning skills of a whole population. We are studying how these skills and other aspects of people's lives, in youth and later, affect their health as they grow older. We think that you will be able to help in answering the question of how people age successfully. It doesn't matter if you don't remember doing the Survey in 1947. If you were born in 1936 and were at school on June 4th 1947 you took part in it.

The LBC1936 study is run by the University of Edinburgh. It is funded by the research charity *Research Into Ageing* which is a part of *Help the Aged*. The team of researchers is listed at the end. They are all internationally-recognised experts in their fields. We hope you will want to take part in this special study.

I enclose a leaflet to tell you some more about the LBC1936 study. There is also a reply slip to send back to us in the pre-paid envelope (no stamp is needed). If you indicate your interest on the reply form it does not commit you to taking part: we will contact you with further details of the study and you can ask any questions. You can also indicate on the form if you'd rather not be contacted. If you are interested in the project Dr Michelle Taylor, our lead researcher, will telephone you to discuss it further. If you decide to take part Dr Taylor will invite you along to the new 'state of the art' Wellcome Trust Clinical Research Facility at the Western General Hospital to have some simple physical measures taken, and do a survey of thinking skills. It will take just one morning or afternoon, whichever suits you better. When people join the study they will be kept up to date with how it is going and will be informed about the results.

We hope to meet you soon and look forward to welcoming you as a member of the LBC1936.

Yours sincerely,

Professor Ian J. Deary, Study Director

The team of investigators on the project is,

Professor Harry Campbell, Department of Public Health, University of Edinburgh
Professor Ian J. Deary, Department of Psychology, University of Edinburgh
Professor David Porteous, Department of Medical Genetics, University of Edinburgh
Dr John Starr, Department of Geriatric Medicine, University of Edinburgh
Dr Peter Visscher, Institute of Biology, University of Edinburgh
Professor Lawrence Whalley, Department of Mental Health, University of Aberdeen
Dr Valerie Wilson, Scottish Council for Research in Education, University of Glasgow

The project is funded by,

Research Into Ageing

The project is administered at,

Lothian Birth Cohort 1936 Study, University of Edinburgh, 7 George Square, Edinburgh,
EH8 9JZ



INFORMATION SHEET

Lothian Birth Cohort 1936 Study

You are invited to take part in the Lothian Birth Cohort 1936 (LBC 1936) Study.

What is the study about?

In June 1947, all children living in Scotland and born in 1936 underwent a verbal reasoning test that measured their thinking skills. We now wish to see how important thinking skills at age 11 years were in determining health and thinking skills at age 68-69 years.

We would like to find out what are the important influences on the change in thinking skills over a lifetime. For instance, if we knew what kinds of things help you to keep your memory in old age, we could see what could be done to prevent the kind of memory problems that affect many people as they get older.

What does the study involve?

The kinds of things we think might be important for any individual are your health, what work you did and what education you had. In addition, we think that 'genetic' factors may have important effects that can only be seen in large numbers of people.

If you agree to take part in the study we will ask you about your education, work and health. We will also measure some simple things like how fast you can walk a short distance, your blood pressure, your vision and how fast you can breathe out.

To measure how your memory and other thinking skills are at the moment, we will ask you to do some simple mental tests. Asking you questions and completing the tests will take around three hours.

We would also like to take some blood to store so that it can be tested for different genes later on. The blood stored for gene testing will be kept completely anonymous as these tests are of no importance for your health as an individual. However, these gene tests are important for us to understand why some people are more likely than others to have problems with their memory.

Will the information remain confidential?

Yes. The information we collect is completely confidential. Your agreement to take part in this study is purely voluntary and does not affect any care or treatment you receive at the hospital. You can withdraw at any time you like without giving any reason to the tester. Dr Elizabeth MacDonald, Consultant Physician, Royal Victoria Hospital, Edinburgh is available if you would like further independent advice about the study.

Would you like further information? **Contact us on 0131 651 1303.**

LBC
1936

LBC1936 appointment letter at wave 1

DATE

NAME

ADDRESS

ADDRESS

POSTCODE

LBCNUMBER

Dear PARTICIPANT

LOTHIAN BIRTH COHORT 1936 APPOINTMENT

Thank you for agreeing to take part in the LBC 1936 Study. I confirm that your appointment will take place on

DATE OF APPOINTMENT at **TIME**

in the **Wellcome Trust Clinical Research Facility (WTCRF)** at the **Western General Hospital**.

What do I need to bring?

1. Spectacles – if you wear them – for both distance and reading.
2. A contact phone number – the name and number of someone who can be reached while you are at the clinic, if necessary.
3. A list of your current medication(s).

How long will it take?

The appointment should last no more than 4 hours. There will be breaks for refreshments.

Travel

Directions to the Western General Hospital and Wellcome Trust Clinical Research Facility are enclosed. Please contact me if you wish to travel by taxi, and I will make arrangements for you. We shall reimburse you for your travel expenses if you wish.

Who can I phone if I have any questions?

Please contact me on **0131 651 1303** if you wish to change the appointment, or if you have any questions.

I look forward to meeting you and welcoming you as a member of the LBC 1936 study.

Yours sincerely

Alan Gow

LBC1936 study research co-ordinator

Consent Form
Lothian Birth Cohort 1936 Study

If you wish to discuss this project or have any queries, please do not hesitate to contact

Dr John Starr
Department of Geriatric Medicine
Royal Victoria Hospital
Craigleith Road
Edinburgh
Tel 0131 537 5000

Consent

I agree to participate in this study.

I have read Information Sheet and Consent Form and had the opportunity to ask questions about them.

I agree for relevant information about this aspect of the study to be sent to my General Practitioner.

I understand that I am under no obligation to take part in this study and that a decision not to participate will not affect my treatment from the hospital or from my own doctor.

I understand that I have the right to withdraw from this study at any stage without giving a reason and that this will not affect my treatment in any way.

I understand that this is non-therapeutic research from which I cannot expect to derive any benefit.

I understand that the information is confidential and that it is not available to any person outside the research team.

Signature of

Subject.....

Name of Subject (please

print).....

Date.....

Signature of

Investigator.....

LBC1936 questionnaire letter at wave 1

DATE

NAME

ADDRESS

ADDRESS

POSTCODE

LBCNUMBER

Dear NAME

Thank you very much for taking part in the Lothian Birth Cohort 1936 study. I hope you enjoyed your visit to the Wellcome Trust Clinical Research Facility and found the study interesting.

As part of the study we would like to gather some information about you, your family, and the things you have done throughout your life (like the type of work or activities you have taken part in), as it is believed these things may have an impact on later thinking and memory skills. We would also like you to describe your typical diet over the past 2-3 months.

To add to the information you have already given us, we would be most grateful if you could find some time to complete the enclosed questionnaires. The questionnaires should take no more than 90 minutes to complete, but please fill them out at your own pace. There is no need to complete the questionnaires in a single session. Feel free to complete one part and fill out other parts later. More detailed instructions are included in the questionnaire booklets. Once you have answered all of the questions, please send all the questionnaires back in the pre-paid envelope provided.

On behalf of the Lothian Birth Cohort 1936 team, I would like to thank you once again for taking part in this important study, and we look forward to receiving your response.

Yours sincerely

Professor Ian J. Deary
Study Director

Appendix F - LBC1936 Phenotype Collection at Wave 1

Research into Ageing Research Grant
Determinants of normal cognitive ageing in surviving participants of the
Scottish Mental Survey 1947

Protocol for phenotype collection in the LBC1936 - Wellcome Trust Clinical Research Facility

Introduction and welcome to LBC1936 Study and consent

Background information

Social and medical history and medications

including years of education, qualifications attained, marital status, self (and spouse) occupation and retirement details, address at age 11, number of rooms, in/outdoor toilet, current living arrangement, smoking and alcohol consumption, history of disease

Hospital Anxiety and Depression Scale (HADS)

Mini-Mental State Examination (MMSE)

Cognitive tests

Logical Memory I (WMS-III)

Verbal Fluency

NART & WTAR

Digit Symbol (WAIS-III)

Digit Span Backward (WAIS-III)

Simple and Choice Reaction Time

Logical Memory II (WMS- III)

Block Design (WAIS-III)

Verbal Paired Associates (WMS- III)

Spatial Span (WMS-III)

Symbol Search (WAIS-III)

Letter-Number Sequencing (WAIS-III)

Matrix Reasoning (WAIS-III)

Verbal Paired Associates (WMS-III)

Inspection Time

Moray House Test

Medical

Physical examination

height, weight, visual acuity, 6m walk time, sit-to-stand, demi-span, head circumference, activities of daily living, blood pressure, lung function (FEV1, FVC, FER, PEF), grip strength, and menopause details (women only)

Blood Tests

full blood count, coagulation, biochemistry including thyroid function and lipids and a sample for storage for genetic analysis

Appendix G - Food Frequency Questionnaire version 7.0

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Scottish Collaborative Group Food Frequency Questionnaire version 7.0



Diet questionnaire for adults

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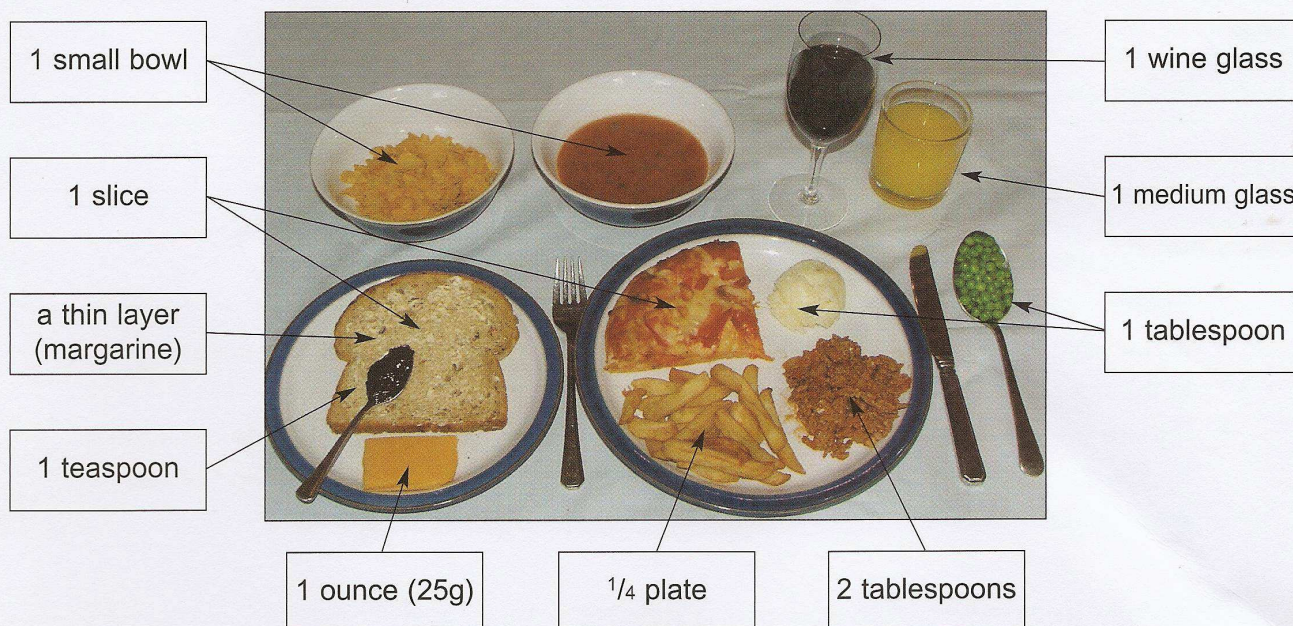


Thank-you for agreeing to complete this questionnaire, which should take around 20 minutes to complete.

Please take a few minutes to read the instructions carefully.

We would like you to describe your typical diet over the last 2-3 months. This should include your main meals, snacks and all drinks apart from water which you have at home or away from home e.g. at work, at restaurants or cafes and with friends and family.

The questionnaire lists 175 foods and drinks, and for each one a measure is listed to help you estimate how much you usually have. The photograph below gives examples of some of these measures:



How to complete the questionnaire

For **every line** in the questionnaire you need to tick **one box** in the table.

- If you almost never have the food, please tick the first box (Rarely or never).
- If you have the food only a few times a month, please tick the next box (1-3 per month)
- If you have one measure of the food several times a week but not every day, please tick one of the weekly choices (1 per week, 2-3 per week or 4-6 per week)
- If you have the food every day, please tick one of the daily choices (1 per day, 2-3 per day, 4-6 per day or 7+ (i.e. 7 or more) per day)
- For a few foods you may have more than one measure on several days a week but not every day. For these foods please use the daily choices which give approximately the same total intake per week, e.g. for 8-10 measures per week please tick 1 per day, and for 11-25 measures per week please tick 2-3 per day

The example below shows the answers for someone who has five slices of bread every day, half a pint of milk (i.e. two $\frac{1}{4}$ pints) every day, one small bowl of soup once a week, three tablespoons of mashed potato three days a week (i.e. 9 measures per week, equivalent to approximately 1 per day), but never has wine:

Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
Bread	1 slice								✓	
Milk	$\frac{1}{4}$ pint							✓		
Soup	1 small bowl			✓						
Mashed potato	1 tablespoon						✓			
Wine	1 wine glass	✓								

- Please use a **black** or **blue** pen to complete the questionnaire.
- Please make sure that the ticks do not cross any of the lines of the grid.
- If you want to change an answer, simply cross out your first tick and add another one in the right box
- If there are any foods or drinks that you eat once a week or more which do not appear on the questionnaire, please list them in section 21 ('other foods') at the end of the questionnaire.

It is very important that you put a tick on every line.

If you rarely or never have a food, please make sure that you tick the first box.

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
1. Breads										
Bread (including toast and sandwiches)	1 medium slice									
Bread roll or bun	1 roll or bun									
Croissants, butteries or garlic bread	1 roll or 2 slices									
Other breads (pitta, naan, soft tortillas)	1 pitta or 1/2 naan									
Which type(s) of bread do you usually eat? Please tick one or more boxes white <input type="checkbox"/> brown/granary <input type="checkbox"/> wholemeal <input type="checkbox"/>										
2. Breakfast cereals										
Cornflakes, Special K, Rice Krispies etc.	1 small bowl									
Bran Flakes, Sultana Bran, All Bran etc.	1 small bowl									
Shredded Wheat, Weetabix etc.	1 biscuit									
Coco Pops, Frosties, Sugar Puffs, Crunchy Nut Cornflakes etc	1 small bowl									
Muesli (all types)	1 small bowl									
Porridge or Ready Brek	1 small bowl									
3. Milk (including milk in drinks and on cereals, but not in cooked foods)										
Full fat milk	1/4 pint									
Semi-skimmed milk	1/4 pint									
Skimmed milk	1/4 pint									
Soya milk	1/4 pint									
Dried milk or creamer	1 teaspoon									
4. Cream and yogurt										
Low fat yogurt (plain or fruit)	1 pot (125 ml)									
Full fat yogurt (e.g. Greek yogurt)	1 pot (125 ml)									
Low calorie yogurt (plain or fruit)	1 pot (125 ml)									
Fromage frais (plain or fruit)	1 pot (125 ml)									
Cream (all types)	1 tablespoon									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
5. Cheese										
Full fat hard cheese (e.g. Cheddar, Wensleydale, Gouda)	1 ounce (25g) or 1 slice									
Medium fat cheese (e.g. Edam, Brie, Camembert, Feta, cheese spreads)	1 ounce (25g) or 1 slice									
Full fat cream cheese (e.g. Philadelphia, Boursin, Danish Blue)	1 ounce (25g) or 1 tablespoon									
Low fat cheese (e.g. low fat cream cheese, low fat hard cheese)	1 ounce (25g) or 1 tablespoon									
Cottage cheese (all types)	1 tablespoon									
6. Eggs										
Boiled or poached eggs	1 egg									
Fried eggs	1 egg									
Scrambled eggs or omelette	1 egg									
7. Meats (excluding meat substitutes e.g. Quorn or soya protein)										
Mince or meat sauce (e.g. bolognese)	2 tablespoons									
Sausages (pork, beef or frankfurters)	1 sausage									
Burgers (beef, lamb, chicken or turkey)	1 burger									
Beef (roast, casserole, grilled or fried)	2 slices, 1 steak or 2 tablespoons									
Pork or lamb (roast, casserole, grilled or fried)	2 slices, 1 chop or 2 tablespoons									
Chicken or turkey (roast, casserole, grilled or fried)	2 slices, 1/2 breast or 1 wing or thigh									
Bacon or gammon	1 medium slice									
Liver, liver sausage or liver pate	1 serving									
Haggis or black pudding	1 slice or 2 tablespoons									
Meat or chicken pies, pasties or sausage roll	1 individual pie or 1 roll									
Cold meats (e.g. corned beef, ham, chicken roll)	1 slice									
Salami or continental sausage	1 slice									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
8. Fish										
Fish fingers	1 finger									
White fish (e.g. haddock, plaice, scampi) fried or cooked in batter	1 small fillet or 1 serving									
Grilled, poached or baked white fish	1 small fillet									
Smoked white fish	1 small fillet									
Fish cakes, fish pie	1 cake or 2 tablespoons									
Fried oily fish (e.g. salmon, herring, fresh tuna or mackerel)	1 small fillet									
Grilled, poached or baked oily fish	1 small fillet									
Smoked oily fish (kipper, mackerel or salmon)	1 small fillet or 1 slice									
Canned salmon	1 tablespoon									
Tinned tuna	1 tablespoon									
Sardines, pilchards or rollmop herrings	2 small fish or 1 large fish									
Prawns, crab etc.	1 tablespoon									
Mussels, oysters, cockles, scallops	1 tablespoon									
9. Potatoes, Rice and Pasta										
Boiled or baked potatoes	1 medium or 1/2 large									
Mashed potatoes	1 tablespoon									
Oven chips or potato waffles	1/4 plate or 1 waffle									
Home-cooked chips	1/4 plate									
Chips from a chip shop or restaurant	1/4 plate									
Roast or fried potatoes	1/4 plate									
White rice	1 tablespoon									
Brown rice	1 tablespoon									
Pasta (all types) or couscous	1/4 plate									
Noodles (all types)	1/4 plate or 1 pot									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
10. Savoury foods, Soups and Sauces										
Pizza	1 slice or 1/2 a small pizza									
Quiche or savoury flan	1 slice									
Savoury pancakes	1 pancake									
Baked beans	1 tablespoon									
Nut roast, nut burgers or vegetable burgers	1 slice or burger									
Quorn products (all types)	1 tablespoon, slice or sausage									
Soya beans, TVP, Tofu or soya meat substitute	1 tablespoon or 1 sausage									
Other beans (kidney butter, chick peas)	1 tablespoon									
Lentils (excluding soup)	1 tablespoon									
Soups (home-made)	1 small bowl									
Soups (tinned)	1 small bowl									
Soups (dried or instant)	1 small bowl or mug									
Gravy	1 tablespoon									
Tomato-based sauces (e.g. for pasta)	1 tablespoon									
Other savoury sauces (white, cheese etc.)	1 tablespoon									
Bottled sauces (e.g. ketchup)	1/2 tablespoon									
Mayonnaise or salad cream	1 teaspoon									
Oil and vinegar dressing	1 teaspoon									
Pickled vegetables and chutneys	1 teaspoon or 1 pickle									
11. Vegetables (including fresh, frozen and tinned vegetables)										
Mixed vegetable dishes (e.g. stir-fry, curry)	1 tablespoon									
Tinned vegetables (all kinds)	1 tablespoon									
Peas or green beans	1 tablespoon									
Carrots	1 tablespoon									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
Cabbage (all kinds)	1 tablespoon									
Brussels sprouts	1 tablespoon									
Broccoli	1 tablespoon									
Spinach or spring greens	1 tablespoon									
Leeks or courgettes	1 tablespoon									
Cauliflower, swede (neeps) or turnip	1 tablespoon									
Sweetcorn	1 tablespoon or 1 piece									
Onions	1 tablespoon or 1/2 onion									
Tomatoes	1/2 medium or 2 small									
Sweet peppers	1/2 pepper									
Other salad vegetables (lettuce, cucumber etc.)	2 leaves or 4 slices									
Potato salad	1 tablespoon									
Coleslaw or other veg. salads in dressing	1 tablespoon									
12. Fruit (including fresh, cooked frozen and tinned fruits)										
Fresh fruit salad	1 tablespoon									
Tinned fruit (all kinds)	1 tablespoon									
Apples	1 fruit									
Bananas	1 fruit									
Oranges, satsumas and grapefruit	1 small or 1/2 large fruit									
Pears	1 pear									
Peaches or nectarines	1 fruit									
Kiwi fruit	1 fruit									
Dried fruit (e.g. raisins, dates or figs)	1 tablespoon or 1 oz. (25g)									
All other fruits (grapes, strawberries, melon etc.)	1 tablespoon or slice									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
13. Puddings and desserts										
Milk-based puddings (e.g. rice, semolina)	1 small bowl									
Sponge puddings (jam, steamed, syrup etc.)	1 small bowl									
Gateaux or cheesecake)	1 slice									
Fruit-based puddings (pies, tarts, crumbles)	1 pie, 1 slice or 2 tablespoons									
Mousse, blancmange trifle, meringue	1 meringue or 2 tablespoons									
Custard or other sweet sauces	2 tablespoons									
Wrapped ice creams (Cornetto, Solero, Magnum etc.)	1 ice-cream									
Other ice cream (all flavours)	1 scoop or small tub									
14. Chocolates, Sweets, Nuts and Crisps										
Chocolate bars (e.g. Mars, Dairy Milk)	1 bar or 2 oz. (50g)									
Chocolate sweets, toffees or fudge	2 sweets									
Boiled sweets or mints	2 sweets									
Fruit gums, pastilles, jellies or chewy sweets	2 sweets									
Salted nuts (peanuts, cashews etc.)	1 small pack or 1 oz (25g)									
Unsalted nuts	1 small pack or 1 oz (25g)									
Crisps	1 small bag									
Reduced fat crisps	1 small bag									
Other savoury snacks (Quavers, tortilla chips, popcorn etc.)	1 small bag									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
15. Biscuits										
Plain (e.g. Rich Tea, digestive)	1 biscuit									
Sweet (e.g. ginger, custard creams)	1 biscuit									
Shortbread	1 biscuit									
Chocolate-coated biscuits	1 biscuit									
Savoury biscuits (crackers, crispbread)	1 biscuit									
Oatcakes	1 biscuit									
Cereal bars, flapjacks	1 bar or slice									
16. Cakes										
Plain cakes (madeira, ginger etc.)	1 medium slice									
Sponge cake with jam, cream or icing	1 medium slice									
Fruit cake	1 medium slice									
Pastries, doughnuts or muffins	1 piece									
Pancakes or scones	1 pancake or scone									
17. Spreads										
Jam, honey or marmalade	1 teaspoon									
Yeast or meat extract (Marmite, Bovril etc.)	1/2 teaspoon									
Peanut butter or chocolate spread	1 teaspoon									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

How many teaspoons of table sugar do you use each day in drinks and on cereals and deserts? (If you do not use any table sugar, please enter 0)

Please make sure that you have put a tick on every line before leaving this page

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Food	Measure	Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day
18. Beverages and soft drinks										
Tea (regular)	1 cup or mug									
Herbal, fruit or decaffeinated tea	1 cup or mug									
Instant coffee (regular)	1 cup or mug									
Decaffeinated coffee	1 cup or mug									
Filter, espresso or cappuccino coffee	1 cup or mug									
Pure fruit juice (orange, apple etc.)	1/2 medium glass									
Tomato juice	1/2 medium glass									
Blackcurrant squash (e.g. Ribena)	1 medium glass									
Other fruit squash	1 medium glass									
Diet fizzy drinks (Cola, lemonade etc.)	1 can									
Regular fizzy drinks	1 can									
Mineral water	1 medium glass									
Tap water (not in other drinks)	1 medium glass									
Hot chocolate	1 cup or mug									
Horlicks or Ovaltine	1 cup or mug									
19. Alcoholic drinks										
Low alcohol lager or beer	1/2 pint									
Dark beer (Export, bitter or stout)	1/2 pint									
Light beer (lager or continental beers)	1/2 pint									
White wine	1 wine glass									
Red wine	1 wine glass									
Sherry, port etc.	1 sherry glass									
Spirits or liqueurs	1 pub measure									
Alcopops (e.g. Bacardi Breezer)	1 bottle									
Cider	1 bottle or 1/2 pint									
		Rarely or never	1-3 per month	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

Please make sure that you have put a tick on every line before leaving this page

20. Spreads and oils

Do you use any butter, margarine or other spread or oil on bread?

Yes ☐

No ☐

If yes, please give full details of the type(s) you use most often (e.g. *St Ivel Golden Churn 69% fat spread*)

office code

office code

How much do you normally spread on one slice of bread?

(an example of a thin layer is shown in the photograph on the front cover)

a scrape ☐

a thin layer ☐

a thick layer ☐

Do you use any fat or oil for home frying or cooking?

Yes ☐

No ☐

If yes, please give full details of the type(s) you use most often (e.g. *Costcutter pure vegetable oil*)

office code

office code

21. Other foods

Please enter details of any foods or drinks which you have **more than once a week** which you have not included in the questionnaire above

Food or drink description	Amount usually consumed	1 per week	2-3 per week	4-6 per week	1 per day	2-3 per day	4-6 per day	7+ per day

22. Vitamin, mineral and food supplements

Please give as full details as possible of any supplements

	Brand name and strength (e.g. Boots A-Z; Holland and Barrett Vitamin C 500 mg)	Amount usually taken per week (e.g. 7 tablets, 2 teaspoons)
Vitamins or multivitamins		
Cod liver oil or other oil		
Bran or wheatgerm		

23. Any other information or comments on your diet

Date of completing questionnaire _____

office code

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Thank-you very much for completing this questionnaire.

Please return it in the reply-paid envelope provided.

Appendix H - Scree Plots for the Cognitive Factors

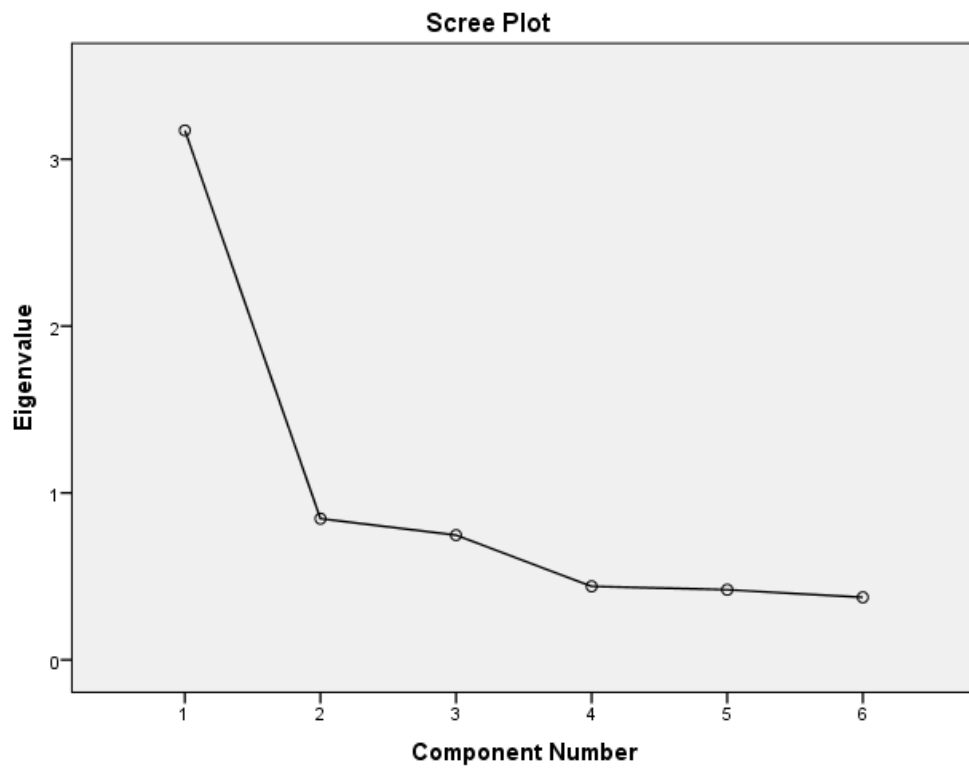


Figure 3.1 The scree plot for general cognitive ability (g) displaying inflexions that would justify retaining one component

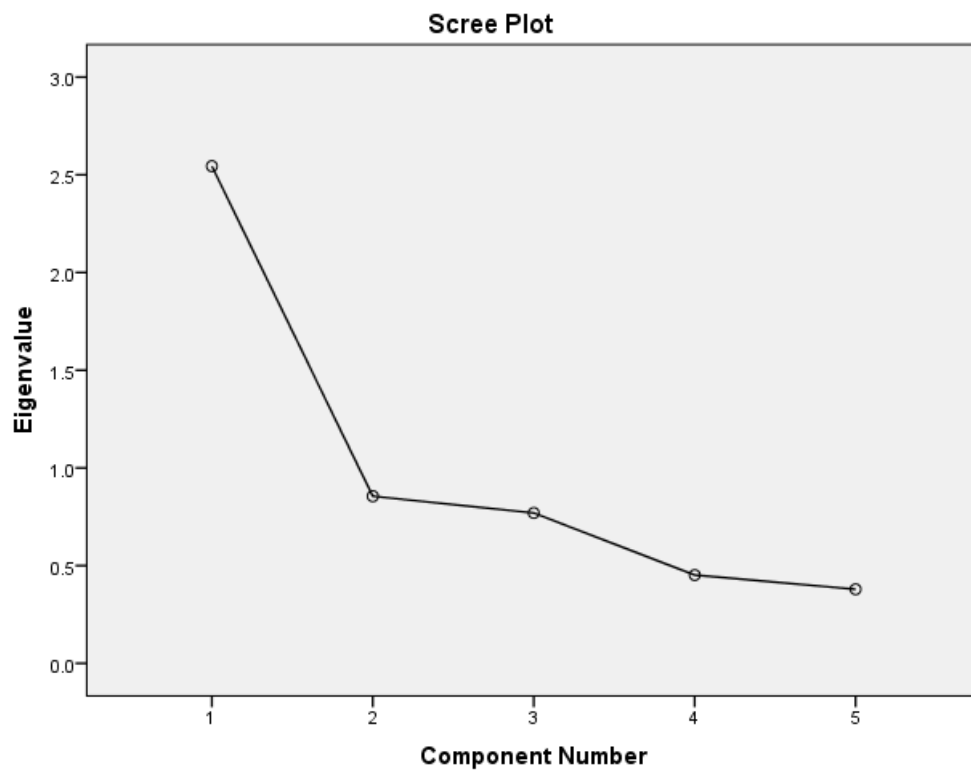


Figure 3.2 The scree plot for processing speed displaying inflexions that would justify retaining one component

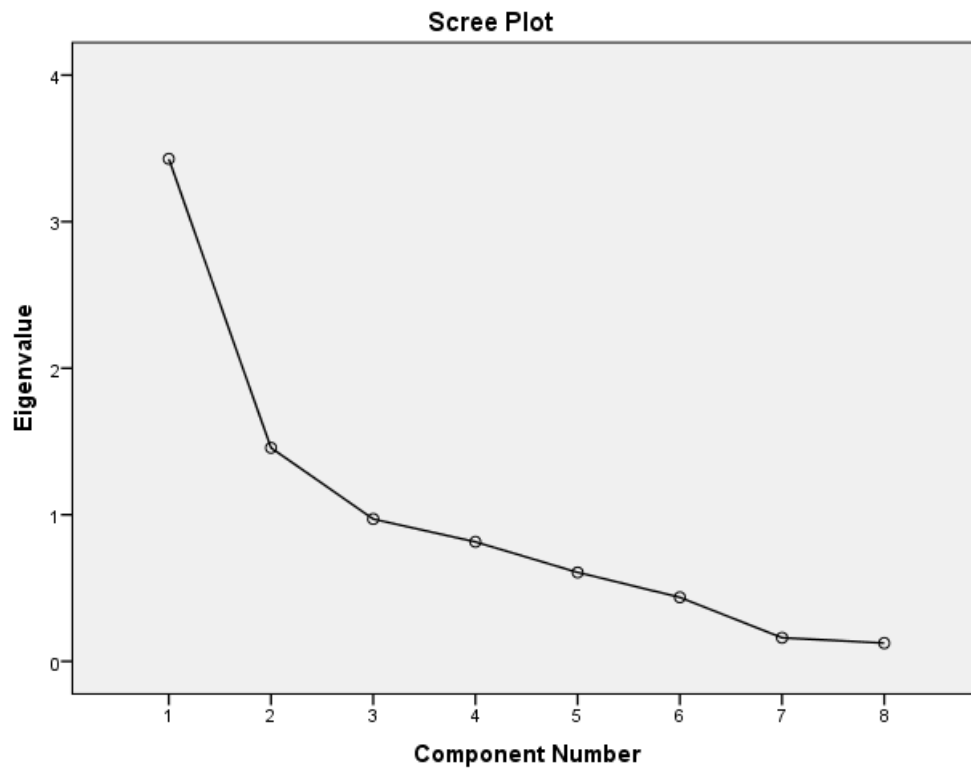


Figure 3.3 The scree plot for memory displaying inflexions that would justify retaining one component